VAPPU RANTALAIHO

The Initial Treatment Strategy and the Long-term Outcome of Early Rheumatoid Arthritis with Special Interest in the FIN-RACo Trial and the Current Finnish Practice

■

ACADEMIC DISSERTATION
To be presented, with the permission of
the board of the School of Medicine of the University of Tampere,
for public discussion in the Main Auditorium of Building M,
Pirkanmaa Hospital District, Teiskontie 35,
Tampere, on June 15th, 2012, at 12 o'clock.

UNIVERSITY OF TAMPERE

UNIVERSITY
OF TAMPERE

ACADEMIC DISSERTATION
University of Tampere, School of Medicine
Tampere University Hospital, Department of Internal Medicine and Centre for Rheumatology
Finland

Supervised by
Docent Markku Korpela
University of Tampere
Finland
Professor Timo Möttönen
University of Turku
Finland

Reviewed by
Docent Pekka Kurki
University of Helsinki
Finland
Docent Jukka Martio
University of Tampere
Finland

Distribution
Bookshop TAJU
P.O. Box 617
33014 University of Tampere
Finland

Tel. +358 40 190 9800
Fax +358 3 3551 7685
taju@uta.fi
www.uta.fi/taju
http://granum.uta.fi

Cover design by
Mikko Reinikka

Acta Universitatis Tamperensis 1737
ISBN 978-951-44-8822-1 (print)
ISSN-L 1455-1616
ISSN 1455-1616

Acta Electronica Universitatis Tamperensis 1208
ISBN 978-951-44-8823-8 (pdf)
ISSN 1456-954X
http://acta.uta.fi

Tampereen Yliopistopaino Oy – Juvenes Print
Tampere 2012

To the Rheumatologists, Nurses, and Patients of the FIN-RACo Trial

CONTENTS

ABSTRACT

Background. The natural course of rheumatoid arthritis (RA) leads through joint inflammation to progressive joint damage and lost functional ability, elevated incidence of work disability and even increased mortality. Effective treatment with disease modifying antirheumatic drugs (DMARDs) has been shown to prevent or delay this progression. Thus, an early and aggressive treatment of RA is recommended internationally. In Finland, mainly due to beneficial 2- and 5-year results of a national multicenter study, the Finnish Rheumatoid Arthritis Combination Therapy Trial (FIN-RACo), a combination of 3 DMARDs and a small dose glucocorticoid (GC) is recommended as the initial treatment in active RA. In this study we aimed to elucidate the long-term effects and safety of such aggressive initial treatment by analysing the 11-year follow-up results of the FIN-RACo Trial. We also wanted to clarify how DMARDs are currently used in early RA in Finland and whether the possible change in treatments may have affected the incidence of work disability (WD) in early RA.

Methods. In the FIN-RACo study 199 patients with early active RA were randomized to treatment with a combination of methotrexate (MTX), sulfasalazine (SASP), and hydroxychloroquine (HCQ) with prednisolone (FIN-RACo group) or treatment with a single DMARD (initially, SASP) with or without prednisolone (SINGLE group). The treatment in both groups aimed at remission. After 2 years, the treatment strategy became unrestricted. At 11 years, function was assessed with the Health Assessment Questionnaire (HAQ), and remission with the American College of Rheumatology (ACR) criteria **(I)**. The radiographs of hands and feet, as well as of large joints were assessed and scored according to the Larsen method **(II)**. In the second part of the study, data for all new Finnish RA patients was collected

from a nationwide register maintained by the Social Insurance Institution (SII) from 1.1.2000 to 31.12.2007. Patient cohorts were analyzed in 2-year time periods (2000-01, 2002-03, 2004-05, 2006-07) and DMARDs purchased by them during the first year after the diagnosis were registered **(III)**. For the patients available to labour force at the time of the diagnosis the incidence of continuous WD up to 31 Dec 2008 was clarified **(IV)**.

Results. At 11 years, 138 patients were assessed (68 in the FIN-RACo group and 70 in the SINGLE group). The mean ± SD HAQ scores were 0.34 ± 0.54 in the FIN-RACo group and 0.38 ± 0.58 in the SINGLE group (p = 0.88). ACR remission was achieved by 37% (95% CI: 26 to 49) of the FIN-RACo group and by 19% (95% CI: 11 to 29) (p = 0.017) of the SINGLE group **(I)**. The radiographs of hands and feet were available in 65 patients in each group at baseline and at 11 years. The mean change from baseline to 11 years in Larsen score was 17 (95 % CI: 12 to 26) in the FIN-RACo group and 27 (95 % CI: 22 to 33) in the SINGLE group (p = 0.037). Respectively 87% (95% CI: 74 to 94) and 72% (95% CI: 58 to 84) of the patients in the FIN-RACo and the SINGLE groups had no erosive changes in large joints at 11 years **(II)**. From the SII database 14 878 (68.0% female, 62.6% RF-positive) patients with a new diagnosis of RA between 2000-07 were identified. In the first cohort single DMARD treatment (56.1%) was the most commonly used strategy during the first 3 months and SASP (63.0%) the most commonly used DMARD during the first year. In the last cohorts the respective treatments were combination DMARDs (55.3%) and methotrexate (69.0%). The change in treatment strategies and in DMARDs used was highly significant (p <0.001 for linearity) **(III)**. From the same database, 7 831 (71% female, 61% RF-positive) not pensioned patients were

identified. During the first 2 years the incidence of RA related continuous WD was 8.9 %, 9.4 %, 7.2 %, and 4.8 % ($p < 0.001$ for linearity) **(IV)**.

Conclusions. Targeting remission with tight clinical controls results in good functional, clinical and radiographic outcomes in most RA patients. However, compared to initial single-DMARD therapy, initial combination DMARDs results in higher rates of patients achieving strict ACR remission and in lower radiographic progression even in the long term. During this millennium in Finland, increasingly active treatments have been adopted in the treatment of early RA and the incidence of continuous work disability has declined.

TIIVISTELMÄ

Varhaisen nivelreuman hoitostrategia ja pitkäaikaistulokset - FIN-REKO-tutkimuksen opetukset ja nykyinen suomalainen lääkehoitokäytäntö

Tausta. Nivelreuman luonnollinen kulku johtaa tulehduksen kautta nivelten tuhoutumiseen, toiminta- ja työkyvyn alenemiseen ja lisääntyneeseen kuolleisuuteen. Antireumaattisten lääkkeiden on todettu estävän, tai ainakin hidastavan tätä taudinkulkua, ja niinpä varhainen ja aggressiivinen hoito antireumaattisilla lääkkeillä on nykyään kansainvälisesti suositeltu hoitostrategia nivelreumassa. Suomessa, suurelta osin kansallisen monikeskustutkimuksen, FIN-REKO:n (Finnish Rheumatoid Arthritis Combination Therapy Trial, FIN-RACo) suotuisten 2- ja 5-vuotistulosten ansiosta, aktiivisessa nivelreumassa aloitushoidoksi suositellaan kolmen antireumaattisen lääkkeen ja pieniannoksisen kortisonin yhdistelmähoitoa. Nykyisessä tutkimuksessa halusimme tutkia tämän aggressiivisen aloitushoidon pitkäaikaisvaikutuksia ja turvallisuutta analysoimalla FIN-REKO-tutkimuksen 11 vuoden seurantatulokset. Lisäksi pyrimme kartoittamaan kuinka antireumaattisia lääkkeitä käytetään Suomessa varhaisessa nivelreumassa, ja onko mahdollisesti aikaisempaa aktiivisemmilla hoitokäytännöillä voitu vähentää pysyvää työkyvyttömyyttä.

Menetelmät. FIN-REKO-tutkimuksessa 199 varhaista nivelreumaa sairastavaa potilasta satunnaistettiin saamaan joko metotreksaatin (MTX), sulfasalatsiinin (SASP), hydroksiklorokiinin (HCQ) sekä prednisolonin yhdistelmähoitoa (FIN-REKO-ryhmä) tai yksittäistä antireumaattia (aloittaen SASP:lla) joko prednisolonin kanssa tai ilman sitä (SINGLE-ryhmä). Hoito molemmissa ryhmissä tähtäsi remissioon. Kahden vuoden jälkeen hoidot olivat vapaat. Yhdentoista vuoden

jälkeen toimintakykyä kartoitettiin erillisellä kyselykaavakkeella [Health Assessment Questionnaire (HAQ)] ja remissiota American College of Rheumatology (ACR) kriteereillä **(I)**. Käsien, jalkojen ja suurten nivelten röntgenkuvat analysoitiin Larsenin menetelmällä **(II)**. Tutkimuksen toisessa osassa kerättiin Kansaneläkelaitoksen (Kela) rekisteritiedoista kaikki uuden nivelreumadiagnoosin 1.1.2000 - 31.12.2007 saaneet potilaat. Potilastiedot analysoitiin kaksivuotiskohorteittain (2000-01, 2002-03, 2004-05, 2006-07) ja potilaiden ensimmäisen vuoden aikana ostamat antireumaatit rekisteröitiin **(III)**. Lisäksi analysoitiin diagnoosihetkellä työkykyisten potilaiden jatkuvan työkyvyttömyyden ilmaantuvuus vuoden 2008 loppuun mennessä **(IV)**.

Tulokset. FIN-REKO-tutkimuksen 11 vuoden käynnille osallistui 138 potilasta (68 FIN-REKO- ja 70 SINGLE-ryhmissä). HAQ keskiarvo ± SD oli 0.34 ± 0.54 FIN-REKO- ja 0.38 ± 0.58 SINGLE-ryhmissä (p = 0.88). ACR remissiossa oli 37% (95% CI: 26, 49) FIN-REKO potilaista ja 19% (95% CI 11, 29) (p = 0.017) SINGLE potilaista **(I)**. Käsien ja jalkojen röntgenkuvat oli otettu 65 potilaasta kummassakin ryhmässä tutkimuksen alussa ja 11 vuoden kohdalla. Larsen scoren keskimääräinen muutos tällä välillä oli 17 (95 % CI: 12, 26) FIN-REKO- ja 27 (95 % CI: 22, 33) SINGLE-ryhmissä (p = 0.037). Isot nivelet olivat säilyneet normaaleina 87%:lla (95% CI: 74, 94) FIN-REKO- ja 72%:lla (95% CI: 58, 84) SINGLE-ryhmien potilaista 11 vuoden kohdalla **(II)**. Kela:n rekisteristä saatiin 14 878 nivelreumaan vuosina 2000-07 sairastuneen potilaan tiedot (68.0% naisia, 62.6% RF-positiivisia). Varhaisimmassa kohortissa ensimmäisen kolmen kuukauden aikana reumalääkkeen yksittäishoito oli yleisin hoitostrategia (56.1%) ja SASP yleisimmin käytetty antireumaatti ensimmäisen vuoden aikana (63.0%). Viimeisessä kohortissa vastaavat hoidot olivat antireumaattien yhdistelmähoito

(55.3%) ja MTX (69.0%). Muutos hoitostrategioissa ja antireumaattien käytössä oli tilastollisesti hyvin merkitsevä ($p < 0.001$ lineaarisuudelle) **(III)**. Samasta rekisteristä kerättiin 7831 (71% naisia, 61% RF-positiivisia) diagnoosihetkellä työkykyistä potilasta. Kohorteissa kahden vuoden aikana nivelreumasta johtuvan, jatkuvan työkyvyttömyyden ilmaantuvuudet olivat 8.9 %, 9.4 %, 7.2 %, and 4.8 % ($p < 0.001$ lineaarisuudelle) **(IV)**.

Yhteenveto. Aktiivinen, remissioon pyrkivä hoitostrategia tuottaa hyvän kliinisen ja radiologisen tuloksen useimmilla potilailla. Kuitenkin alkuvaiheessa kolmen lääkkeen yhdistelmähoitoa saaneilla potilailla on vielä pitkäaikaisseurannassakin enemmän remissioita ja vähemmän radiologista etenemistä kuin alkuvaiheessa yksittäishoitoa saaneilla. Tällä vuosituhannella varhaisen nivelreuman hoito on Suomessa muuttunut entistäkin aktiivisemmaksi. Samaan aikaan varhaisesta nivelreumasta johtuvan pitkäaikaisen työkyvyttömyyden ilmaantuvuus on alentunut.

LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following original communications, referred to in the text by their Roman numerals I-IV. In addition, some unpublished data are presented.

I Rantalaiho V, Korpela M, Hannonen P, Kautiainen H, Järvenpää S, Leirisalo-Repo M, Hakala M, Puolakka K, Julkunen H, Luosujärvi R, Möttönen T; FIN-RACo Trial Group. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. Arthritis Rheum. 2009 May;60(5):1222-31.

II Rantalaiho V, Korpela M, Laasonen L, Kautiainen H, Järvenpää S, Hannonen P, Leirisalo-Repo M, Blåfield H, Puolakka K, Karjalainen A, Möttönen T; FIN-RACo Trial Group. Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. Arthritis Res Ther. 2010;12(3):R122.

III Rantalaiho V, Kautiainen H, Virta L, Korpela M, Möttönen T, Puolakka K. Trends in treatment strategies and the usage of different disease-modifying anti-rheumatic drugs in early rheumatoid arthritis in Finland. Results from a nationwide register in 2000-2007. Scand J Rheumatol. 2011 Jan;40(1):16-21.

IV Rantalaiho V, Kautiainen H, Järvenpää S, Virta L, Korpela M, Möttönen T, Puolakka K. Work disability caused by early rheumatoid arthritis is declining. Results from a nationwide Finnish register in 2000-2008. Ann Rheum Dis. 2012; in press.

ABBREVIATIONS

ACPA	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ANOVA	Analysis of variance
ARA	American Rheumatism Association
ATC	Anatomical Therapeutic Chemical classification
BeSt	Behandel-Strategieën Trial
BMI	Body mass index
CAMERA	Computer Assisted Management in Early Rheumatoid Arthritis Trial
CARDERA	Combination Anti-Rheumatic Drugs in Early Rheumatoid Arthritis Trial
CI	Confidence interval
CIMESTRA	Cyclosporine, Methotrexate, Steroid in RA Trial
COBRA	Combinatietherapie Bij Rheumatoïde Arthritis Study
CRP	C-reactive protein
CyA	Cyclosporine
DAS	Disease Activity Score
DC	Dendritic cell
DMARD	Disease modifying antirheumatic drug
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FIN-RACo	Finnish Rheumatoid Arthritis Combination Therapy Trial
GC	Glucocorticoid
GDP	Gross domestic product
GEE	Generalized estimating equation
GH	Global health
HAQ	Health Assessment Questionnaire
HCQ	Hydroxychloroquine
HLA	Human leukocyte antigen
HR	Hazard ratio
ICD-10	International classification of diseases
IgG	Immunoglobulin G
IgM	Immunoglobulin M

IL-1	Interleukin-1
IL-6	Interleukin-6
IP	Interphalangeal
IQR	Interquartile range
MCP	Metacarpophalangeal
MDA	Minimal disease activity
MHC	Major histocompability complex
MTP	Metatarsopahalangeal
MTX	Methotrexate
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
PAD	Peptidyl-arginyl-deiminase
PIP	Proximal interphalangeal
RA	Rheumatoid arthritis
RAI	Ritchie Articular Index
RF	Rheumatoid factor
RR	Risk ratio
SASP	Sulfasalazine
SD	Standard deviation
SDAI	Simplified Disease Activity Index
SE	Shared epitope
SII	Social Insurance Institution
SIR	Standardized incidence ratio
SJC	Swollen joint count
SMR	Standardized mortality ratio
SNP	Single nucleotide polymorphism
Swefot	Swedish Pharmacotherapy study
TICORA	Tight Control for Rheumatoid Arthritis Trial
TJC	Tender joint count
TNF-α	Tumour necrosis factor α
VAS	Visual Analogue Scale
WD	Work disability

INTRODUCTION

Up till the mid 1980s a misapprehension of the allegedly benign nature of the natural course of rheumatoid arthritis (RA) led widely to a conservative treatment strategy based on non-steroidal anti-inflammatory drugs (NSAIDs) and bed rest, as well as to avoidance of at that time available, often toxic or ineffective disease modifying antirheumatic drugs (DMARDs) (Sokka et al. 2008). Through increasing evidence, however, the true nature of RA as a disabling disease was unravelled and the urge for more aggressive treatment strategies grew evident (Wilske and Healey 1989). Thus, during the 1990s, earlier and continuous (when needed, sequential) use of different DMARDs became increasingly common (Fries 1990). Still, while a great improvement to earlier treatments, real life proved this "sawtooth" strategy ineffective in many patients, and clinicians turned to creative use of different DMARD combinations even though the evidence of their use was at that point sparse (Borigini and Paulus 1995).

As the treatment of RA had traditionally been active in Finland (Sievers et al. 1963, Isomäki and Martio 1976, Luukkainen et al. 1977), the Finnish rheumatologists were aware of the dilemma of these mediocre treatment results and, as early as in 1993, initiated the Finnish Rheumatoid Arthritis Combination Therapy Trial (FIN-RACo) comparing initial combination DMARD strategy to initial single DMARD strategy in early RA (Möttönen et al. 1999). So far the results have favoured the initial combination strategy without any increase in adverse effects; at 2 years the remission rate was higher and radiographic progression lower (Möttönen et al. 1999) in the combination group compared to the single group, and especially the patients with a delay to treatment benefited from the combination treatment (Möttönen et al. 2002). And despite the release of the treatments after 2 years, at 5

years the combination group patients had less radiographic damage in small joints (Korpela et al. 2004) as well as in cervical spine (Kauppi et al. 2009), and better preserved working ability (Puolakka et al. 2004) than the single group patients.

The results of FIN-RACo Trial as well as of other studies have led to the contemporary consensus of treating RA actively, and aiming at remission or low disease activity (Current Care Guideline 2009, Smolen et al. 2010a, Smolen et al. 2010b). As these recommendations, however, are based on rather short follow-up trials (Gaujoux-Viala et al. 2010) and while RA is a chronic disease requiring lifelong treatment, there is a demand for studies elucidating the long term efficacy and safety of different treatment strategies. Also, earlier cohort studies have shown, that despite the current recommendations, in real world the treatment of RA may be suboptimal (Edwards et al. 2005, Carli et al. 2006, Neovius et al. 2011a). Therefore, before giving new recommendations it would be essential to clarify how the old ones are followed.

In the present study, first the long-term effects and safety of an initial combination-DMARD treatment compared to a single-DMARD treatment in early RA from the 11-year data of the FIN-RACo Trial were studied. In the second part of this study the aim was to clarify from a register-based data the DMARD strategies prescribed to all Finnish new RA patients during the present millennium, as well as the incidence of work disability in those patients.

REVIEW OF THE LITERATURE

1. Rheumatoid arthritis

1.1 Definition of rheumatoid arthritis

The concept of rheumatoid arthritis (RA) comprises a variety of clinical phenotypes, all of which share the predisposition of chronic, systemic auto-inflammation presenting mainly in synovial joints and leading to joint destruction. In clinic, rheumatologists base their diagnosis of RA on patient history, as well as on clinical, radiological and laboratory findings. Also, mainly for scientific purposes, various classification criteria of RA have been produced. The original aim of these criteria has been to differentiate RA from other rheumatic diseases with high specificity and sensitivity in clinical trials. During the past decades, the most often applied criteria have been The American College of Rheumatology (ACR; formerly The American Rheumatism Association) 1987 revised criteria for the classification of rheumatoid arthritis (Table 1) (Arnett et al. 1988).

Table 1. The American College of Rheumatology (ACR; formerly The American Rheumatism Association) 1987 revised criteria for the classification of rheumatoid arthritis (Arnett et al. 1988)

	Present for over 6 weeks
1. Morning stiffness in joints lasting at least 1 hour	+
2. Arthritis of 3 or more joints observed by a physician	+
3. Arthritis of the proximal interphalangeal (PIP), metacarpophalangeal (MCP), or wrist joints	+
4. Symmetric arthritis	+
5. Rheumatoid nodules	
6. The presence of rheumatoid factor	
7. Radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints	

According to these criteria the disease can be classified as RA if 4 of the above 7 criteria are fulfilled.

The ACR 1987 criteria are particularly valid for differentiating established RA from other rheumatic diseases. However, as they underline the findings in hand joints and emphasize such late features of RA as rheumatoid nodules and radiographic changes, they have been criticized for not recognizing early RA. As increasing evidence has proven the early and active treatment of RA critical for improved outcomes (Cush 2007), new criteria were urged for. Therefore, in 2010, ACR and the European League Against Rheumatism (EULAR) formulated a new set of criteria to be used in newly presenting patients with at least one swollen joint that may not be better explained by some other disease (Aletaha et al. 2010).

Table 2. The parameters and scoring system used in 2010 ACR/EULAR classification criteria for newly presenting arthritis (Aletaha et al. 2010)

A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

Score ≥6 represents definite RA in a patient with at least one swollen joint that may not be explained by another disease.

These criteria assess and score the number and size of swollen joints, serology, acute phase reactants and symptom duration; a score ≥6 represents definite RA (Table 2). Patients with typical erosive radiographic findings may also be diagnosed as having RA, even if they do not fulfil these criteria. Still, whatever the contemporary classification criteria, the physicians make, and should make, their diagnosis as well as treatment decisions on clinical grounds.

1.2 Aetiology of rheumatoid arthritis

The aetiology of rheumatoid arthritis remains unclear. Presumably a genetic predisposition together with an unknown, even varying, triggering environmental factor induces the outset of this chronic, progressive autoimmune disease. It also appears evident that RA consists of several subtypes of disease with partly specific, partly shared predisposing and triggering factors.

Studies in monozytogic twins have shown that genetic factors explain approximately half of the variation of RA prevalence between different populations. Thus far the best-described genetic factor associated with increased susceptibility to, and severity of, RA, is a so-called shared epitope (SE). It consists of a specific amino acid sequence (glutamine-leucine-arginine-alanine-alanine) found in certain HLA-DRB1 alleles (*0101, *0102, *0401, *0404, *0405, *0408, *1001, *1402) in the MHC class II molecules on the surface of antigen presenting cells (APCs) and activated T-cells. The mechanism through which the SE predisposes the individual to RA is, however, still unknown. Besides SE, the HLA-DR4 allele has been found to be more common in RA patients than in general population. Other genetic factors predisposing to RA have been discovered amongst various single nucleotide polymorphisms (SNPs), some of which are also connected to an increased risk of other autoimmune diseases (Kvien et al. 2009).

Nevertheless, none of the abovementioned genetic factors alone causes RA; an external factor is needed to generate the disease start. Therefore, quite self-evidently, different infections have served as usual suspects for triggering RA; yet, hitherto, in extensive research none has been found guilty. Conversely, cigarette smoking has been confirmed to predispose to the development of RA (Heliövaara et al. 1993, Klareskog et al. 2006, Verstappen et al. 2011) and is also associated with more severe disease and worse responsiveness to traditional and biological disease modifying anti-rheumatic drugs (DMARDs) (Hyrich et al. 2006, Saevarsdottir et al. 2011). Recently, periodontal disease has been linked to etiopathogenesis of RA (Detert et al. 2010). Other environmental risk factors for RA proven in some cohorts have been coffee consumption, high body mass index (BMI), as well as occupational exposure to mineral oils and to anthracite, asbestos and silica dust. Sex hormones have also been conjectured to RA, as the starting age of menarche, the use of oral contraceptives, pregnancies, and menopause have all, in different ways, been connected to the risk and severity of RA (Kvien et al. 2009).

1.3 Pathogenesis of rheumatoid arthritis

Knowledge of the pathogenetic process behind RA is still fragmented. Nevertheless, the essential phenomenon of RA is the inflammation of the synovial joints. Normally, inflammation is the body's defence mechanism against external attackers, where inflammatory cells recognize foreign antigens and strive to destroy their source. In auto-inflammatory diseases, such as RA, the inflammatory process, however, is directed against the body's own tissues. This requires a breakdown of the immunological tolerance, which normally prevents the inflammatory cells from recognizing self-antigens (Schulze-Koops et al. 2009).

The cells involved in auto-inflammation of RA represent both innate and humoral immunology. Dendritic cells (DCs) represent antigens to naïve T cells, which, if co-stimulation occurs, then differentiate into effector T cells. They produce different cytokines, some of which activate B cells into secreting autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). This in turn leads to immune complex formation and complement activation. Other cytokines enhance the endothelial permeability contributing to recruitment of T cells as well as other effector cells such as neutrophils and macrophages. This activates the production of further proinflammatory cytokines and chemokines and as well as the osteoclastogenesis, all leading to tissue destruction. The origin of this cascade is thus far unknown, and as the antigen initiating the process leading to clinical RA most probably differs between individuals, and as it may precede the clinical manifestation of RA by years, it might never be solved (Firestein 2005).

1.3.1 Autoantibodies in rheumatoid arthritis

In the 1940s and 1950s, the discovery of rheumatoid factor (RF) generated the idea of RA being an autoimmune disease. RF is an autoantibody targeting the Fc part of human IgG, and found in the serum of many RA patients (60-70 %); less often in normal population (5 %). RF is mainly presenting as IgM and forms immune complexes, which activate the complement. This increases the capillary permeability and stimulates the synthesis of chemotactic factors, which, in turn, are thought to enrol inflammatory cells to joints. However, as on one hand, RF is found in healthy individuals and in other autoimmune as well as in infectious diseases, and, as on the other hand, not all RA patients are seropositive for RF, it alone cannot be held responsible for the whole pathogenetic cascade in RA. Still, on average, RF positive disease is more aggressive, and leads to earlier joint damage and extra-

articular manifestations, than RF negative one (Bukhari et al. 2002, Taylor et al. 2011).

A more specific autoantibody found in the sera of 50-70 % of RA patients, but seldom in healthy individuals, is the one targeting citrullinated peptides. Citrullination of arginine residues to non-naturally occurring citrulline emerges through deamination, which is catalyzed by enzymes called peptidyl-arginyl-deiminases (PADs). This reaction requires the presence of calcium and is induced by inflammation, especially when significant cell death is present. Citrullination can occur in any inflammatory state, but the formation of anti-citrullinated protein antigens (ACPA) appears to be specific for RA and depend on the host's genotype, especially on the presence of shared epitope (Taylor et al. 2011). How ACPA act in the pathogenesis of RA is unknown, but ACPA-positive RA leads to radiographic progression more often than ACPA-negative one (Bukhari et al. 2007, Syversen et al. 2008).

1.3.2 Proinflammatory cytokines in rheumatoid arthritis

Leukocytes, especially T cells, macrophages, and stromal cells all secrete cytokines. The balance between proinflammatory and anti-inflammatory cytokines as well as the expression of their corresponding receptors defines the degree of inflammation. Numerous different cytokines exist and their distribution varies in different types of arthitidem, but the current understanding of the therapeutic effects of certain anti-cytokine therapies emphasizes the importance of tumour necrosis factor α (TNF-α), interleukin-6 (IL-6), and IL-1 in maintaining chronic inflammation and leading to tissue destruction in RA (Karmakar et al. 2010).

1.4 Epidemiology of rheumatoid arthritis

Worldwide, the prevalence of RA varies between 0.3-1.1 % with the lowest figures in South-European and developing countries and the highest in the US, especially amongst some Native American tribes (Kvien et al. 2009). In Finland, 0.8 % of the population suffers from this disease which has a yearly incidence of 34/100 000 (Kaipiainen-Seppänen 2000). RA is more prevalent in females than in males (3:1) and its incidence rises with increasing age, plateauing after the age of 60. In the last decades, a decreasing trend in the incidence of RA was found (Doran et al. 2002, Kaipiainen-Seppänen and Kautiainen 2006); however this variation appears cyclic as the latest findings show again an increase in the incidence of RA (Gabriel and Michaud 2009).

1.5 Natural course of rheumatoid arthritis

Locally, auto-inflammation is expressed most often in the small and middle-sized joints, especially the proximal interphalangeal (PIP), metacarpophalangeal (MCP) and wrist joints in the hand as well as the metatarsopahalangeal (MTP) and ankle joints in the feet. Inflammatory cells invade the synovium causing first hyperplasia and later formation of invasive and destructive tissue ("pannus"). The clinical signs of this phenomenon are swelling, stiffness and tenderness of the affected joints. When not treated, the disease progresses and spreads to other, even large, joints. Other local manifestations of the disease include inflammation of the tendon sheaths and bursae. The rate of progression varies amongst individuals and may have several phenotypes (Graudal 2004). Spontaneous remission, healing of the disease, however, is rare and would even question the authenticity of the diagnosis.

If allowed to continue, the inflammation causes progressive destruction of the cartilage and adjacent bony structures; changes detectable by radiographies (Abu-

Shakra et al. 1998). In the beginning of the disease, acute inflammation, and later, the destruction of the joints both lead to augmented disability (Kirwan 2001) threatening the patients' function in daily practices, as well as working ability (Pincus et al. 1984).

Extra-articular manifestations of chronic inflammation in RA include rheumatoid, subcutaneous, nodules, secondary Sjögren's syndrome, pulmonary nodules or interstitial fibrosis, pleuritis, pericarditis, episcleritis and scleritis, Felty's syndrome, as well as vasculitis, at times manifested as mononeuritis multiplex. As in many systemic autoimmune diseases the chronic activation of autoreactive B cells increases the risk of lymphoma, being twofold in RA compared to general population (Kaiser 2008). Chronic, systemic inflammation causes elevation of acute phase proteins such as serum amyloid A, which through accumulation predisposes the patient to amyloidosis; most commonly manifesting as proteinuria, and later, renal failure (Kvien et al. 2009). The most frequent and thus the most important complication of chronic inflammation is, nevertheless, the cardiovascular disease. Systemic inflammation as such appears to accelerate atherosclerosis, even overpowering the traditional risk factors, which, however, also contribute to the total risk of cardiovascular diseases in RA (Kitas and Gabriel 2011). Today, the increased mortality found in RA patients is mainly explained by cardiovascular diseases (Sihvonen et al. 2004).

Besides the comorbidities related to the disease itself, the treatments used in RA pose distinct problems, most of which are transitory. Nevertheless, immunosuppressive medications increase the risk of serious infections, and glucocorticoids additionally predispose the patients to osteoporosis, hypertension,

diabetes mellitus, and cataract. However, all of these are features of high-dose glucocorticoid treatment and rare when small doses are used (Da Silva et al. 2006).

2. Outcome measures in rheumatoid arthritis

2.1 Clinical outcomes

2.1.1 The core set

Quantifying the disease activity of RA is important when evaluating the efficacy of a given treatment for a single patient in daily clinical practice, but in clinical studies it becomes mandatory. Not only is it essential to quantify the results of a study to convince the readers; to enable comparisons between different data sets, it is necessary to use similar methods internationally. For this purpose, a core of different estimates has become established (Tugwell and Boers 1993).

2.1.1.1 Joint assessment

In clinical examination the joints are assessed with respect to swelling, tenderness in palpation and in motion, and with respect to limitation of motion or deformity. Specific joint counts are used for swollen joints, where the number of joints assessed may vary from 28 to 66; and for tender joints, from 28 to 68 joints (Table 3). In most joint counts both swelling and tenderness of each joint are scored on a 0-1 scale; however, in the Ritchie articular index part of the joints are assessed in units (the PIP, MCP, MTP, temporomandibular, sternoclavicular and acromioclavicular joints), and the tenderness is graded on a 0-3 score (Ritchie et al. 1968).

2.1.1.2 Visual Analogue Scales

Three different Visual Analogue Scales (VAS) from 0 to 100 millimetres have been developed to measure the patient's evaluation of general health, as well as of

pain, and the physician's estimation of global disease activity. These scales are easy and fast to use and give valuable information of the disease course of an individual patient, even though, as subjective measures, might not be that reliable when comparing different patients.

Table 3. Joints assessed in different joint counts (Pincus and Sokka 2006).

Joint	66/68 joints	Ritchie index	44 joints	42 joints	28 joints
Atlantoaxial		+			
Temporomandibular	+	+			
Sternoclavicular	+	+	+		
Acromioclavicular	+	+	+		
Shoulder	+	+	+	+	+
Elbow	+	+	+	+	+
Wrist	+	+	+	+	+
Metacarpophalangeal (1-5)	+	+	+	+	+
Proximal interphalangeal (1-5)	+	+	+	+	+
Distal interphalangeal (1-5)	+				
Hip (tenderness only)	+	+		+	
Knee	+	+	+	+	+
Talocrural	+	+	+	+	
Subtalar		+			
Midtarsal	+	+			
Metatarsophalangeal (1-5)	+	+	+	+	
Proximal interphalangeal (1-5)	+				

2.1.1.3 Acute phase reactants

The current systemic inflammation may be assessed by measuring the acute phase reactants; the erythrocyte sedimentation rate (ESR) with the Westergren method or the C-reactive protein (CRP) with nephelometry. They are non-specific markers of inflammation, but correlate well with disease activity and progression. However, their sensitivity is not optimal as normal values are often found, even in the presence of high disease activity (Sokka and Pincus 2009).

2.1.2 Disease activity score (DAS)

Despite their importance in assessing the RA disease activity, the single core estimates may give too fragmented and even conflicting a picture of the disease activity. Therefore, especially for studies comparing the efficacy of different treatment outcomes, various composite indices have been created (van der Heijde and Östergard 2009).

Today, the most common estimates of disease activity, especially in studies comparing the efficacy of certain medical agents, are the disease activity scores assessing 28 joints (DAS28) or 44 joints (DAS), which are counted from the formulas:

DAS28 = 0.56 * √(tender28) + 0.28 * √(swollen28) + 0.70 * ln(ESR) + 0.014 * (GH) (Prevoo et al. 1995).

DAS = 0.55938 * √(RAI) + 0.06465 * √(swollen44) + 0.330 * ln(ESR) + 0.00722 * (GH) (van der Heijde et al. 1990)

In these formulas “tender28” and “swollen28” represent the number of tender and swollen joints out of the 28 joint assessments, “GH” the patient’s global assessment of disease activity on VAS of 100mm, “RAI” the Ritchie Articular Index (53 joints

in 26 units, graded for tenderness), and “swollen44” the number of swollen joints in the 44 joint assessment.

2.1.3 Remission

In general, remission means the state of absence of disease activity in patients with a chronic illness, with the possibility of returning disease activity. In RA, remission predicts preserving the functional capacity as well as retarding the radiographic progression (van Tuyl et al. 2010a). However, various definitions still exist for such an essential outcome measure (Mäkinen et al. 2005a). In clinical practice, the valid definition is no active joints (in particular no swollen joints), normal acute phase reactants, and no radiographic progression (Mäkinen et al. 2005a). In the present era of the modern imaging possibilities some authors have gone even further by suggesting that remission should not allow any inflammatory activity in power doppler or in magnetic resonance imaging (Brown et al. 2008).

In clinical studies the definition of remission has to be unambiguous. Numerical limits of disease activity are commonly used; DAS28 below 2.6 or DAS below 1.6 are considered to represent the state of remission (Prevoo et al. 1995). Their limitation for clinical practice is the fact that they still do allow some disease activity (Mäkinen et al. 2005b).

More stringent criteria for remission are the ones developed in 1982 by the ARA (nowadays ACR) (Table 4) (Pinals et al. 1981). They include six requirements, five of which should be fulfilled for the patient to be in remission. However, the use of these criteria is not stable; in some studies the requirement of no fatigue may be omitted and the number of requisite criteria may vary. In 2011 ACR and EULAR published new criteria for defining remission in clinical trials (Table 5) (Felson et al.

2011). These criteria are thought to work in clinical studies, but in clinical practice they still allow some disease activity.

Table 4. The ACR criteria for remission in RA (Pinals et al. 1981)

Five or more of the following requirements must be fulfilled for at least two consecutive months	
1.	Duration of morning stiffness not exceeding 15 minutes
2.	No fatigue
3.	No joint pain (by history)
4.	No tenderness or pain in motion
5.	No soft tissue swelling in joints or tendon sheaths
6.	ESR (Westergren method) < 30mm/hour for a female or <20mm/hour for a male

Table 5. The 2011 ACR and EULAR criteria for remission in RA (Felson et al. 2011)

To be in remission the patient must at any time point fulfil either of the two following definitions:
Boolean-based definition
The patient must have all of the following:
Tender joint count ≤ 1 (including also the feet and ankles in addition to the 28 joint count)
Swollen joint count ≤ 1 (including also the feet and ankles in addition to the 28 joint count)
CRP ≤ 1mg/dl
Patient global assessment ≤ 1 (on a 0-10 scale)
Index-based definition
Simplified Disease Activity Index (SDAI) score ≤ 3.3 (SDAI is counted as the simple sum of the TJC (using 28 joints), SJC (using 28 joints), patient global assessment (0-10 scale), physician global assessment (0-10 scale), and CRP level (mg/dl).

2.1.4 Minimal disease activity

As, especially in established RA, the state of remission may be difficult to achieve, other, near-remission clinical outcome measures have been developed. Of these, minimal disease activity (MDA) is defined to be present if the patient has no swollen joints, no tender joints and an ESR ≤ 10 mm/hour or if she or he fulfills at least 5 of the following 7 criteria: swollen joint count ≤ 1 (0-28), tender joint count ≤ 1 (0-28), HAQ ≤ 0.5 (0-3), VAS for pain ≤ 20 (0-100), patient's global assessment of disease activity ≤ 20 (0-100), physician's global assessment of disease activity ≤ 15 (0-100), ESR ≤ 20 mm/hour (Wells et al. 2005).

2.1.5 Functional ability

A disease causing joint swelling, stiffness, pain, and damage leads inevitably to decreased function. In RA the functional capacity is most often assessed by the Health Assessment Questionnaire (HAQ), which includes 20 questions assessing 8 different areas of function: dressing, arising, eating, walking, hygiene, reaching, gripping, and performing tasks (Fries et al. 1980). The answers to each question are scored from 0 to 3; the score is 0 if the activity can be performed without difficulty, 1 if the patient has some difficulty, 2 if the patient has much difficulty or needs help or devises, and 3 if the patient is unable to perform that activity. The mean value of the highest scores of each 8 subdimensions is counted. The HAQ score of 0 represents normal function, of 0.13-1 mild to moderate disability, 1-2 severe disability and 2-3 very severe disability (Bruce and Fries 2003). The Finnish version of HAQ has been used since the 1990s (Hakala et al. 1994). The HAQ score has been claimed to be the most important single predictive measure of consequent disability and even mortality in RA (Farragher et al. 2007). However, in a large German study by Ziegler et al. (2010) the authors noted that even though all the

physician derived outcomes improved between 1997 and 2007, the patient derived ones, including functional ability, did not.

Table 6. The questions included in the Health Assessment Questionnaire (HAQ)

	Without any difficulty (0)	With some difficulty (1)	With much difficulty (2)	Unable to do (3)
DRESSING AND GROOMING. Are you able to:				
1. Dress yourself, including tying shoelaces and doing buttons?				
2. Shampoo your hair?				
ARISING. Are you able to:				
3. Stand up from a straight chair?				
4. Get in and out of bed?				
EATING. Are you able to:				
5. Cut your meat?				
6. Lift a full cup or glass to your mouth?				
7. Open a new milk carton?				
WALKING. Are you able to:				
8. Walk outdoors on a flat ground?				
9. Climb up five steps?				
HYGIENE. Are you able to:				
10. Wash and dry your body?				
11. Take a tub bath?				
12. Get on and off the toilet?				
REACH. Are you able to:				
13. Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?				
14. Bend down to pick up clothing from the floor?				
GRIP. Are you able to:				
15. Open car doors?				
16. Open jars which have previously been opened?				
17. Turn faucets on and off?				
ACTIVITIES. Are you able to:				
18. Run errands and shop?				
19. Get in and out of a car?				
20. Do chores such as vacuuming or yard work?				

2.1.6 Response measures

In clinical practice the target of the treatment is remission or low disease activity. However, traditional antirheumatic treatments alone seldom succeed in inducing this, and yet they differ from placebo. For clinical studies two valid tools for interpretation of group results during follow-up have been developed, the ACR improvement criteria (Felson et al. 1993) (Table 7) and the EULAR response criteria (van Gestel et al. 1996) (Table 8). The ACR-N describes a continuous percentage the improvement or worsening of a single patient in analogy of the ACR20, ACR50 and ACR70 responses (Bathon et al. 2000).

Table 7. The ACR improvement criteria (Felson et al. 1993)

20 / 50 / 70 % improvement in 5 out of the following 7 core set variables, first 2 required, none allowed to worsen
Tender joint count
Swollen joint count
Acute phase reactant
Patient's assessment of pain
Patient's global assessment of disease activity
Observer's global assessment of disease activity
Patient's assessment of physical disability

Table 8. The EULAR response criteria depending on the DAS/DAS28-value achieved at endpoint and the magnitude of change from baseline (van Gestel et al. 1996)

DAS at endpoint	DAS28 at endpoint	Improvement in DAS or DAS28 from baseline > 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤ 2.4	≤ 3.2	**Good**		
>2.4 and ≤ 3.7	> 3.2 and ≤ 5.1		**Moderate**	
> 3.7	> 5.1			**None**

2.2 Radiographic progression

2.2.1 Small joints of hands and feet

As RA affects first and mainly the small joints, leading to narrowing of the joint spaces and erosive damage to the adjacent bony structures, the radiographs of hands and feet are used to evaluate the degree of joint destruction. In clinical practice, when setting the diagnosis and evaluating the efficacy of treatment, the treating rheumatologist and, if needed, the radiologist estimate the presence of RA related findings and their progression over time. However, in clinical studies more exact evaluations are needed. The two most important methods for this are the Larsen (Larsen et al. 1977) and the Sharp / van der Heijde (van der Heijde 2000) methods.

The Larsen scoring method is based on a set of reference radiographs (Larsen et al. 1977). The MCP I-V and PIP II-V joints as well as IP I joints of the hands, wrists, and IP I and MTP II-V joints of the feet are assessed. Each joint is graded with a scale form 0 to 5; where 0 stands for normal appearance, 1 for slight abnormality, 2 for definite early abnormality, 3 for medium destructive abnormality, 4 for severe destructive abnormality, and 5 for mutilating abnormality. After multiplying the wrist scores by 5, all individual joint scores are summed up, giving thus the maximal total score of 200.

The Sharp / van der Heijde method assesses and grades separately the possible erosions as well as joint space narrowings in hand, wrist and feet joints (van der Heijde 2000). In the hands the maximal total score for erosions is 160 and for narrowing 120, in the feet the respective figures are 120 and 48; thus the maximal total score is 448.

There are some differences between these two main scoring methods. The Sharp/van der Heijde method has been found to be more sensitive to change than the

Larsen score, thus it is able to detect small changes earlier (Bruynesteyn et al. 2002, Guillemin et al. 2005). On the other hand, the Larsen method tends to be more specific than the Sharp/van der Heijde method (Bruynesteyn et al. 2002). Also, in Larsen score the intraobserver reliability is somewhat better than that of the Sharp/van der Heijde method (Sharp et al. 2004, Guillemin et al. 2005).

2.2.2 Large joints and total joint replacements

Even though RA initially affects mainly the small joints of hands and feet, it often spreads to large joints, and in rare cases may start from them. The involvement of large joints disturbs greatly the patient's functional ability (Drossaers-Bakker et al. 2000) and may require operative treatment, especially total joint replacements (Wolfe and Zwillich 1998), causing substantial difficulties and costs both for the patient and for the society. In clinical practice the symptomatic large joints are radiographed and treated accordingly, but in published RA follow-up studies the radiographic assessment of large joints is rare. In one study radiographic damage was found in large joints in 50 % of the patients after 6 years of RA (Kuper et al. 1997) and in another in 54 % of the patients after 12 years of RA (Drossaers-Bakker et al. 2000). Thus far the only validated method for evaluating the radiographic progression in large joints is the Larsen method (Larsen et al. 1977).

2.3 Working ability

Understandably, the cumulative disability, caused by continuous inflammation and consequent damage of the joints, leads to increased work disability. Therefore, one important aim of the treatment of RA is to decrease, or to postpone, work disability. However, as, in addition to disability, working ability depends on numerous other factors, such as the patients' age, psychosocial factors, education and working environment, as well as the socioeconomic and legislative settings of

the surrounding society, interpretation of these studies is challenging. Also, the heterogeneous nature (sick leave, temporary or permanent work disability, employment) and varying definitions (official register data, patient's own announcement) of work disability complicate the matter. Even though the best information on temporal trends of work disability in RA would be achieved by studying longitudinal, population based materials in a fixed setting (Verstappen et al. 2004), many studies are cross-sectional or carried out in small cohorts.

Table 9. Earlier Finnish studies on work disability in RA

First author and year	Type of the study	Number of patients	Disease duration	Work disability rate	Risk factors for work disability
Mäkisara and Mäkisara 1982	Cross-sectional	405	5 years 10 years 15 years	40 % 50 % 67 %	Age, strenuous work, low education, no vocational training
Nissilä et al. 1983	Longitudinal	107	3 years	32 %	
Kaarela et al. 1987	Longitudinal	103	8 years	43 %	Age, strenuous work, severe RA
Jäntti et al. 1999	Longitudinal	103	20 years	80 %	
Sokka et al. 1999a	Longitudinal	86	2 years 10 years	23 % 38%	Physically demanding job, age, number of swollen joints

2.3.1 European studies

In the previous European studies of patients with early RA, 20-50 % of the patients had become work disabled 2 years after the diagnosis (Doeglas et al. 1995, Albers et al. 1999, Sokka et al. 1999a, Barrett et al. 2000), 40-50 % by 10 years (Mäkisara and Mäkisara 1982, Sokka et al. 1999a, Barrett et al. 2000), and 80 % by 20 years after the diagnosis (Jäntti et al. 1999). Similar figures are found in the

earlier Finnish studies on RA and work disability presented in Table 7. However, in more recent studies from Germany (Ziegler et al. 2010) and Sweden (Neovius et al. 2011b), the work disability caused by RA appears to be declining.

2.3.2 North-American studies

Presumably due to differences in social policy, in American studies the early work disability is lower than in European studies; 5-15 % after 2 years of RA, but increasing to 30-50 % after 10 years (Yelin 1992, Wolfe and Hawley 1998). However, in a more recent study, Allaire et al. (2008a) assessed data from a large US national databank between 2002-05. In the 4385 RA patients who had been employed at disease onset and who at assessment had a mean disease duration of 14 years, the prevalence of arthritis-attributed work cessation was 13.6 % in subjects with 1-3 years of disease duration, increasing to 19.0 %, 28.9 %, 28.3%, 38.2 % and 42.2 % after a disease duration of 4-6, 9-11, 14-16, 19-21 and ≥25 years, respectively. Also, 39 % of the patients who had stopped working at some time, returned later to work at least temporarily. Thus, RA still does cause a notable menace to the patients' working ability, but the contemporary risk may be lower than that in the previous decades.

2.3.3 Comparisons between different countries

The intercontinental difference was confirmed by Chung at al (2006), who compared a Finnish cohort of 364 working aged and working RA patients to an US cohort of 269 similar patients. They found the probability to continue working 1, 2, 3 and 4 years after the RA diagnosis to be 92 %, 86 %, 84 % and 80 % in Finland and 92 %, 89 %, 89 % and 84 % in the US, respectively, thus higher than in previous studies. Interestingly, however, the adjusted incidence of work disability was 2.6-fold higher in Finland than in the US, even though the Finnish RA patients

had better functional capacity and global status as well as less pain than the US patients.

In the Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) trial, the authors collected cross-sectional data of 8039 RA patients from 32 countries worldwide (Sokka et al. 2010). In this study, 37 % of the patients who had been working at the time of the first symptoms of RA reported subsequent work disability due to RA. When the 1756 patients with the disease onset during this millennium were analysed separately, the authors found the probabilities to continue working to be 80 % after 2 years of RA and 68 % after 5 years, similarly in high gross domestic product (GDP) (>24K US dollars [USD] per capita) and low-GDP (<11K USD per capita) countries. Patients who stopped working had worse clinical status than the ones who continued to work, in both the high- and the low-GDP countries, with the HAQ-score being the one most important identifier of work disability. Most interestingly, the patients who had become work disabled in the high-GDP countries had significantly better HAQ and DAS28 scores than the patients who continued to work in the low-GDP countries, again stressing the importance of different social security systems' explanatory role.

2.3.4 Work disability in RA compared to general population

Table 10 presents the details of the studies that have compared the prevalence of work disability in RA patients and in general population. As the table shows, the number and inclusion criteria of RA patients, the disease duration, the definition of work disability, the method of data collection, and the definition of general

Table 10. Studies comparing work disability in RA patients and general population

Author	Year of data collection	Country	Method	Number (definition) of patients	Disease duration (mean)	General population	Definition of work disability	Results
Mitchell et al. 1988	1978	US	Interview within the Social Security Survey of Disability and Work. Results extrapolated to the total population	5 652 (Persons reporting both arthritis diagnosis and polyarthritis symptoms)	N.A.	Persons reporting neither arthritis diagnosis nor arthritis symptoms	Interview: Degree of disability (not – moderately – severely disabled) Work status (working – not working)	Polyarthritis patients vs. general population Disabled: 78 % vs. 10 % Working: males: 56 % vs. 89 % females: 31 % vs. 62 %
Yelin 1992	1970-87	US	Data from National Health Interview Surveys. Results extrapolated to the total population	N.A. (Self reported arthritis)	N.A.	Persons without arthritis	Persons out of labour force, self-report	Labour force participation approximately 20 % lower in males and 25 % in females with arthritis than in those without it
Mau et al. 1996	1982-87	Germany	6-year prospective follow-up of a single institute cohort	73 (RA patients, diagnosis ≤ 12months)	7 years	Members of the compulsory German social security insurance (result given only in the Discussion, data source official statistics)	Persons with total cessation of employment due to RA receiving a social security pension	37 % of the patients permanently work disabled due to RA after 7 years of disease duration, steepest decrease within the first 3 years. In general population the annual incidence of permanent work disability 0.6 %
Mau et al. 2005	1993-2001	Germany	Cross-sectional analysis of the National Database of the German Collaborative Arthritis Centres	26 071 (20-59 year-old RA patients)	42 % ≤ 5 years 26 % 6-10 years 32 % > 10 years	Population data from an annual interview survey of 1 % of German households from Federal Statistical Office	Self-administered patient questionnaires on current employment status	Standardized employment ratio 0.78 in all RA patients compared to general population (0.81 in males and 0.76 in females), worse with long disease duration and in former East Germany

N.A. = not available

Table 10. Continues

Author	Year of data collection	Country	Method	Number (definition) of patients	Disease duration (mean)	General population	Definition of work disability	Results
Albers et al. 2001	1991-92	Netherlands	Retrospective/ prospective interview on the patients' socio-economic situation before and after the diagnosis of RA	76 (RA patients who at the time of the diagnosis were working-aged and working)	2.8 years	Dutch population (data source not given)	Interview questions on "to what extent occurs (partial) work disability?" and official registers	51 % of the RA patients became (at least partially) work disabled. Relative risk compared to Dutch population: females 14.5 males 4.1
van Jaarsveld et al. 1998	1996	Netherlands	Since 1990 all one-institute early RA patients randomised to 2 treatment arms, in 1996 interviewed. All working aged respondents included.	211 (Working aged RA patients, data on employment at the time of the diagnosis not given)	< 6 years	Dutch population (national statistics available and used in age groups 25-44 and 45-64 years)	Interview questions on work disability in general and due to RA, hours worked per week	61 % of the patients not working compared to 38 % of the Dutch population (of 45-64 year-old males 63 % and 32 %, respectively).
Chorus et al. 2000	1996	Netherlands	Random sample of 16-59 year-old RA patients from a Dutch Standardised Diagnosis Register of Rheumatic Diseases (a rated sampling to include sufficient number of male and younger patients)	1056 (RA patients, 62 % of the initial cohort)	12 years	Dutch population (official national statistics)	Interview questions on work situation at the time of the diagnosis and currently (Having a paid job equalled labour force participation)	Standardised labour force participation 61.2 % in RA patients (disease duration < 6 years) vs. 65.5 % in general population, in longer disease duration decreased participation in RA patients. At the time of the diagnosis 58.3 % of the patients working, 35.2 % of them later stopped due to RA.
Barrett et al. 2000	1989-92 1994-97	UK	Postal interview of 2 primary–care based inception cohorts (Norfolk Arthritis Register)	Cohort 1: 160 Cohort 2: 134 (Economically active early RA patients)	8 years 4 years	Age, gender and employment status matched controls for the first group	Interview questions changes in employment status since 1989 (hours at work, job title, nature of job, reasons for stopping work, educational attainment)	Cohort 1: work disability rates 14 % 1 y, 26% 2 y, 33 % 5 y, 39 % 10 years after RA diagnosis. Work disability 32 times more likely than in matched controls. Cohort 2: work disability rates 23 % 1 y, 33% 2 years after RA diagnosis

N.A. = not available

population in these studies are very heterogeneous and thus not necessarily comparable. However, all of them show that RA patients have a decreased ability to work compared to the general population (Mitchell et al. 1988, Yelin 1992, Mau et al. 1996, van Jaarsveld et al. 1998, Albers et al. 1999, Barrett et al. 2000, Chorus et al. 2000, Mau et al. 2005).

2.4 Mortality

During the previous decades the mortality of RA patients has been increased compared to general population or matched controls with the standardized mortality ratio (SMR) varying between 1.28 and 2.98 (Doran et al. 2002, Gabriel and Michaud 2009) and the main causes of death being the cardiovascular diseases (Goodson et al. 2005); extra-articular manifestations have been the most significant single risk factor for increased mortality (Gabriel et al. 2003). More recent findings have, however, suggested that the mortality gap between RA patients and population may be narrowing (Sokka et al. 1999b, Kroot et al. 2000, Puolakka et al. 2010, Kapetanovic et al. 2011). Especially the increasing use of methotrexate appears to be protective from premature mortality, underlining the role of inflammation and it's control in the total outcome of the RA patient (Choi et al. 2002, van Nies et al. 2010, Westlake et al. 2010, Mikuls et al. 2011).

3. Drug treatment of early rheumatoid arthritis

As the aetiology and pathogenesis of RA remain unclear, its treatment has long been based on clinical experience of efficacious agents, rather than on true understanding of the pathogenetic mechanisms of the disease. Recently, with the increasing knowledge of the effect of cytokines and inflammatory cells in the pathogenetic cascade of RA, new biological drugs have been developed. At the

same time, the mechanisms of action of the older DMARDs have been at least partly revealed.

3.1 Disease modifying anti-rheumatic drugs (DMARDs)

3.1.1 Methotrexate

Methotrexate (MTX) was originally developed as an anticancer therapy. Therein it inhibits the purine and pyrimidine synthesis via folate antagonism, leading to inhibition of cellular proliferation. In addition to this, in RA, methotrexate appears to have several anti-inflammatory properties; even though the exact mechanisms of the most crucial ones may still remain unclear (Chan and Cronstein 2010).

Due to its good efficacy and favourable safety profile, leading to good treatment continuity, methotrexate has become the anchor drug in RA (Pincus et al. 2003). The results achieved by methotrexate are comparable across different studies. In one study comparing methotrexate, adalimumab and the combination of the two in early RA, by the end of the first year, methotrexate monotherapy had led to an ACR20, ACR50 and ACR70 response in 63%, 46%, and 28 % of the patients, respectively, and up to 21% of the patients achieved DAS28 remission (Breedveld et al. 2006).

Methotrexate is recommended to be started with a small weekly dose and stepwise escalated to up to 20-30 mg per week with a regular monitoring of liver enzymes and complete blood count. Folate supplementation is advocated for reducing toxicity (Visser et al. 2009). Intramuscular or subcutaneous administration increases efficacy and reduces toxicity (Visser and van der Heijde 2009).

3.1.2 Sulfasalazine

In addition to being a frequently used medication of inflammatory bowel diseases, sulfasalazine (SASP) is a well-established DMARD, whose mechanism of action remains, however, unclear (Plosker and Croom 2005). It has been proven

effective in placebo controlled studies (Hannonen et al. 1993, Suarez-Almazor et al. 2000a), and proven to be as effective as methotrexate (Haagsma et al. 1997, Dougados et al. 1999), leflunomide (Smolen et al. 1999), intramuscular gold (Williams et al. 1988), or hydroxychloroquine (Faarvang et al. 1993) in head to head comparisons. The most common side effects of sulphasalazine are gastrointestinal disturbances, headache and elevated liver enzymes; neutropenia being an uncommon but serious complication.

3.1.3 Hydroxychloroquine

Hydroxychloroquine (HCQ) was primarily an anti-malarial drug, but is currently mainly used as a DMARD in RA and in various collagenosis. Its antirheumatic efficacy is moderate, but safety profile favourable, with the most common side effects being mild gastrointestinal disturbance, solar rash, nightmares, and rarely retinopathy (Suarez-Almazor et al. 2000b). In active RA it is currently seldom used as monotherapy but rather as a part of different DMARD combinations.

3.1.4 Other DMARDs

3.1.4.1 Azathioprine

Azathioprine has some antirheumatic potential (Jeurissen et al. 1991). Nowadays in clinical practice it is most often used in the presence of mild renal failure or possible disease features of collagenoses. Side effects such as elevated liver values or nausea are common. In the FIN-RACo trial azathioprine was used as a substitute for MTX.

3.1.4.2 Aurothiomalate

Gold compounds are the first true DMARDs and have been used in the treatment of RA since decades (Kean and Kean 2008). The effect of intramuscular gold may

be good and a substantial portion of patients achieves even remission, however, side effects, such as rash and proteinuria, cytopenias and elevated liver enzymes are not rare, and unfortunately constrain the use of aurothiomalate.

3.1.4.3 Auranofin

The oral gold compound, auranofin has significantly weaker anti-rheumatic effect, yet similar but weaker side effects than aurothiomalate and today has a minor role in the treatment of RA (Kean and Kean 2008). In the FIN-RACo trial auranofin was used as a substitute for HCQ.

3.1.4.4 Cyclosporine

Cyclosporine (CyA) is a calcineurin inhibitor and primarily used as an immunosuppressant after organ transplantations. However, it has also been used as a DMARD with a moderate beneficial effect on clinical activity of RA. It is not recommended for first line use in monotherapy, and in most recent studies it is included as a part of a combination treatment (Kitahara and Kawai 2007). The typical side effects of cyclosporine are impairment of renal function and hypertension.

3.1.4.5 Leflunomide

Leflunomide came to market in the late 1990s for the treatment of RA (Behrens et al. 2011). It has a similar efficacy to sulfasalazine (Smolen et al. 1999) and methotrexate (Cohen et al. 2001). Its most common side effects are liver enzyme elevations and diarrhoea.

3.2 Glucocorticoids

Glucocorticoids (GCs) have extensive anti-inflammatory and immunosuppressive effects (Spies et al. 2010) and they are widely used in RA; the majority of the patients use them at some point, and approximately 60 % more or less continually. GCs retard the radiological progression in early RA (Kirwan et al. 2007) and as they relieve inflammatory symptoms more rapidly than traditional DMARDs, GCs are often used as bridging therapy (Gorter et al. 2010). However, their long-term use is restrained by cumulative side effects such as osteoporosis, diabetes, hypertension, skin atrophy, infections, and cataract.

With local, intra-articular administration of the GCs the symptom relief is fast (Habib et al. 2010) and lasts for one month, on the average. Also, the structural destruction appears to halt (Hetland et al. 2008) and the side effects are less common than with systemically administered GCs.

3.3 Biological treatments

3.3.1 TNF-α-inhibitors

With increasing understanding of the pathogenetic mechanisms behind RA, more tailored treatments, such as TNF-α-inhibitors, have been developed (Firestein 2005). The first TNF-α-inhibitor to come to clinical use in 1999 was infliximab, which is a chimeric (mouse-human), monoclonal antibody against TNF-α (Maini et al. 1999). After that, etanercept, a soluble TNF-α-receptor was introduced (Weinblatt et al. 1999). Adalimumab, a totally human monoclonal antibody against TNF-α was the next one to come to market (Keystone et al. 2004) and under recent years certolizumab-pegol (Smolen et al. 2009) and golimumab (Keystone et al. 2009) have been introduced as well. All of these TNF-α-inhibitors have quite similar therapeutic effects, decreasing the disease activity and retarding the radiographic

progression in many patients (Singh et al. 2009). They are more efficient when used in combination with MTX, possibly due to MTX's reducing effect on the immunogenicity of these therapeutic proteins (Bendtzen et al. 2006). When biologics are used in monotherapy, their efficacy in MTX-naïve patients equals that of MTX monotherapy. Their efficacy toward other manifestations of autoimmunity differs slightly, as does their safety profile (Singh et al. 2009). In general, TNF-inhibition impairs the function of the host defence system, and thus increases the incidence of infections, including opportunistic ones (Singh et al. 2011a, Woodrick and Ruderman 2011). The TNF-α-inhibitors are administered either subcutaneously (adalimumab, certolizumab pegol, golimumab, etanercept) or intravenously (golimumab, infliximab) at different intervals according to their half-life.

TNF-α-inhibitors were first tested in refractory, especially MTX resistant RA, and therefore, in clinical practice, often used in long-standing RA. Under recent years with increasing evidence of the importance of early induction of remission in RA, TNF-α-inhibitors have been studied in early, MTX-naïve RA (Genovese et al. 2002, St Clair et al. 2004, Breedveld et al. 2006) and in clinical practice their introduction has spread to earlier disease.

3.3.2 Others

In addition to TNF-α-inhibitors other biological therapies in RA have come to clinical use. Anakinra is an IL-1 receptor antagonist indicated for treatment of RA (Cohen et al. 2002), but appears less effective than other biologics (Singh et al. 2009). Rituximab is a B-cell depleting agent (anti-CD20), and is especially effective in RF- or ACPA-positive RA and is mainly used in patients failing or having contra-indications to TNF-α-inhibitors (Buch et al. 2011). Abatacept suppresses the rheumatoid inflammation by inhibiting the co-stimulation of T-cells (Kremer et al.

2005). Tocilizumab inhibits IL-6, an important proinflammatory cytokine, and improves the clinical outcomes in RA combined to MTX (Singh et al. 2011b), but also as monotherapy (Nishimoto et al. 2009).

3.4 Treatment strategies

3.4.1 Pyramid strategy

In the 1960s through 1970s, as therapeutic modalities, as well as proper understanding of the course of RA, were lacking, a so-called pyramid treatment strategy was adopted (Kamin and Multz 1969, Bluestone 1970). Aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) were administered regularly; glucocorticoids were used as local, intra-articluar injections, systemic glucocorticoids were reserved for rare cases and for short use. Disease modifying anti-rheumatic drugs (DMARDs); mainly intramuscular gold and antimalarial compounds; were administered only if other treatments failed, and even then, for short terms. Other treatment modalities included bed-rest, physiotherapy and rehabilitation, splinting, synovectomies, and orthopaedic surgery.

3.4.2 Saw tooth strategy

In the 1980s and 1990s, as the false presumption of the good prognosis of RA gave way to more realistic ideas, a more active treatment policy started to prevail (Wilske and Healey 1989). DMARDs were changed to each other sequentially in a so-called saw-tooth method, if the clinical response was not satisfactory or due to side effects (Fries 1990, Sokka et al. 2000).

3.4.3 Combination strategies

The results of earliest studies utilising combinations of different DMARDs were not encouraging. Side effects were common and the increase in efficacy marginal

(Felson et al. 1994). However, with more effective and less toxic agents, new studies assessing the efficacy and safety of different DMARD combinations have been carried out. They can be divided into two main categories. In step-up studies the treatment is started with a single DMARD, but in case of inefficacy intensified by adding another DMARD(s) to the original one. One version of step-up strategy is a treatment response steered strategy. A step-down treatment strategy includes starting multiple DMARDs at the same time, and continuing, or even increasing them until a predetermined time or treatment goal is reached, after which tapering or even stopping one DMARD at a time may be attempted.

3.4.4 Combination treatment trials

Several studies have been carried out comparing treatment with a combination of DMARDs to a treatment with single DMARDs, as well as with using different strategies. Some of these studies are presented in Table 11 (O'Dell et al. 1996, Calguneri et al. 1999, Dougados et al. 1999, Marchesoni et al. 2003, Capell et al. 2007, Saunders et al. 2008) and others below in greater detail.

3.4.4.1 COBRA

In the COBRA study 155 patients with early RA were randomized to receive either initial sulfasalazine monotherapy or a combination of sulfasalazine, high dose prednisolone (starting from 60 mg daily and tapered down and stopped during the first 28 weeks) and methotrexate (tapered and stopped after 40 weeks) (Boers et al. 1997). A pooled index assessing the clinical disease activity was better in the combination group than in the monotherapy group at 28 weeks, but the difference disappeared after prednisolone was stopped. However, the radiographic progression

Table 11. Studies on combination DMARD treatment

Author and year	Number and characteristics of patients	Disease duration	Follow-up	Treatments	Outcome measures		Favours initial combi
O'Dell et al. 1996	n=103 Poor response to at least one earlier DMARD	10 years	2 years	 MTX+SASP+HCQ SASP+HCQ MTX	50% improvement: 77% 40% 33%		+
Calguneri et al. 1999	n=180 Active RA (but SJC 5), not on DMARDs	2.3 years	2 years	 MTX+SASP+HCQ MTX+SASP / MTX+HCQ MTX / SASP /HCQ	ACR remissions: 60% 45% 32%	Radiographic non-progression: 69% 64% 25%	+
Dougados et al. 1999	n=205 Active, DMARD-naïve RA	< 1 year	1 year	 SASP MTX SASP+MTX	Change in DAS: -1.15 -0.87 -1.26	EULAR good response: 34% 38% 38%	
Marchesoni et al. 2003	n=61 Active, DMARD-naïve RA	0.9 years	12 months	 MTX+CsA MTX	Damage score change (0-12mo): 1.9 7.5	ACR20/50/70: 53%/50%/47% 61%/42%/19%	+
Capell et al. 2007	n=165 SASP (6 months) failure (DAS>2.4), willing to participate	1 year	18 months	 MTX+SASP SASP MTX	ACR 20% response (6-18mo): 29% 18% 15%	Remission: 10% 5% 3%	+
Saunders et al. 2008	n=96 Active, DMARD-naïve RA	11.5 months	12 months	 SASP>SASP+MTX>SASP+MTX+HCQ SASP+MTX+HCQ Both groups: targeted (DAS28<3.2) treatment, monthly visits, ia. GCs	Change in DAS28 (0-12mo): -4.0 -3.3	DAS28 remission 45% 33%	

was slower in the combination group at 1 year, at 5 years (Landewe et al. 2002), and possibly even after 11 years (van Tuyl et al. 2010b) than in the monotherapy group. In a short pilot study van Tuyl and colleagues (2008) treated 21 patients with early, active RA with "intensified COBRA strategy" (predisolone starting from 60mg daily, tapered down, but continued throughout the follow-up with 7.5mg daily; MTX 10mg/week; SASP 2g/day; HCQ 400mg/day) and found that 90 % of the patients were in DAS28 remission at 40 weeks.

3.4.4.2 FIN-RACo

In the FIN-RACo trial 199 early, DMARD-naïve, RA patients were randomized to receive for the first 2 years either a triple DMARD combination starting with sulfasalazine, methotrexate, hydroxychloroquine, and low dose prednisolone, or a single DMARD starting with sulfasalazine with or without low dose prednisolone (Möttönen et al. 1999). The aim of treatment in both groups was to achieve remission, and to maintain it. The treatments were intensified according to a predefined protocol and intraarticular GCs were injected to inflamed joints. In case of intolerance, the DMARDs could be switched to others. After 2 years, strict ACR remission was more common in the combination group than in the single group (37% vs. 18%), and radiographic progression slower. The combination group patients also sustained the achieved remission more often than the single group patients (Mäkinen et al. 2007). In patients with very early disease (< 4 months), even single treatment gave satisfactory results, but if the disease duration was longer, combination DMARD strategy was superior (Möttönen et al. 2002). After 2 years the treatments were unrestricted. At 5 years the difference between remissions rates was not significant, but the combination group patients had less radiographic damage than the single group patients (Korpela et al. 2004), which was especially

explained by the slower radiographic progression in the ACPA-negative patients (Mustila et al. 2011). There were also less radiographic changes in the cervical spine in the combination group than in the single group at 2 (Neva et al. 2000) and at 5 years (Kauppi et al. 2009). At 5 years the working capacity was preserved more often in the combination than the single group patients (Puolakka et al. 2004), and especially in those patients who had been in remission at 6 months (Puolakka et al. 2005a).

3.4.4.3 BeSt

In the BeSt study a total of 508 patients with early, DMARD-naïve (prior antimalarials allowed) RA were randomized to four different treatment strategies (Goekoop-Ruiterman et al. 2005). The first treatment group received sequential DMARD monotherapy, the second one step-up combination therapy; in both initial monotherapy groups the treatment was started with MTX 15-30mg weekly. The third group received initially the COBRA regimen (Boers et al. 1997), where prednisolone was tapered from 60mg/day to 7.5mg/day within 7 weeks and in case of persistent low disease activity ($DAS_{44} < 2.4$) stopped after 28 weeks and MTX was tapered to zero after 40 weeks. The fourth group initiated the treatment with a combination of MTX and infliximab; the latter could be tapered down and stopped after 6 months of low disease activity ($DAS_{44} < 2.4$). On the other hand, according to a predefined protocol, with control visits every 3 months, the treatments in all groups were intensified if the treatment response was insufficient ($DAS_{44} > 2.4$). During one year of follow-up, the patients in either original combination group reached earlier functional improvement and had less radiographic damage than the patients of the initial monotherapy groups. Low disease activity ($DAS_{44} < 2.4$) was less common in the sequential monotherapy group (53%) than in either of the

combination groups (71% and 74%). The percentage of patients who had received intraarticular GCs during the first year was higher in the monotherapy groups than in the combination groups (22% and 26% vs. 8% and 13%). However, after 5 years follow up, 48% of the patients were in remission (DAS < 1.6) irrespective of the original randomization group, and 14% were in drug-free remission (Klarenbeek et al. 2011). Additionally, all the clinical outcomes and the rate of radiographic progression were similar between the groups from one year onward, but as the two initial combination group patients had had less radiographic damage during the first year, their cumulative damage by 5 years was smaller than that of the monotherapy patients. At 5 years, 21%, 5%, 11%, and 19% of the patients in the respective groups were using infliximab.

3.4.4.4 TICORA

TICORA was the first study designed especially to differentiate between different treatment strategies (Grigor et al. 2004). There 111 combination-DMARD-naïve patients with RA for less than 5 years were randomized to receive either routine care with control visits every 3 months and treatment adjustments according to the treating physician's judgement; or intensive care, with monthly visits and DAS-steered therapy so, that in case of persisting disease activity (DAS > 2.4) first sulphasalazine monotherapy was changed to a combination of sulphasalazine, MTX and hydroxychloroquine, then the doses were increased and prednisolone added, later the DMARDs could be switched to others. According to the protocol, intraarticular GCs were injected to inflamed joints in the intensive group; in the routine group these were allowed but far less commonly given. During the 18 months follow-up, the patients in the intensive group were using more combination treatments (67% vs. 11%), and had received more intraarticular GCs than the

routine group patients. By the end of the follow-up the intensive group patients had lower disease activity, more DAS-remissions (65% vs. 16%), and less radiographic progression than the routine group patients.

3.4.4.5 CIMESTRA

In the CIMESTRA trial a total of 160 patients with early RA were randomized into two step-up groups: combination group (MTX plus CyA) and monotherapy group (MTX plus placebo-CyA) during the first year (Hetland et al. 2006). Both groups were treated actively by injecting intraarticlar GC injections to all inflamed joints and by increasing the dosage of MTX up to 20mg/week. If swollen joints persisted despite these treatment modifications, CyA or placebo-CyA was introduced. During the second year of the study, CyA or placebo-CyA was tapered to zero and HCQ was added to all patients in order to enable the withdrawal of MTX from patients in sustained remission after 3 years. If an ACR20 response was not achieved, first MTX was changed to parenteral dosing, further SASP was added to form triple therapy, and thereafter a TNF-α-inhibitor was introduced. At 2 years more patients in the combination group had reached an ACR20 and ACR50 response than in the monotherapy group, however, there were no differences in the ACR70 (59% vs. 54%) or DAS-remission (51% vs. 50%) rates or in the radiographic progression. Similar excellent results were gathered after 5 years, when 78% of the patients were in DAS-remission, 56% in ACR-remission, 17% in drug-free remission and 47% had no radiographic progression from baseline (Hetland et al. 2010). The 5-year results did not differ between the original randomization groups, but baseline bone marrow oedema in wrist MRI, the presence of ACPA, as well as the total Sharp-van der Heijde score predicted the radiographic progression at 5 years.

3.4.4.6 CARDERA

In a British multicenter study, the CARDERA, a total of 1391 patients with active RA of less than 2 years duration were screened, and 467 randomized to double-blindly receive either MTX, MTX and CsA, MTX and prednisolone, or a combination of all three, and followed up for 2 years (Choy et al. 2008). The primary outcome measure was radiographic progression. In the MTX group 29% of the patients developed new erosions, while 17%, 16%, and 13% did so in the MTX+CsA, MTX+prednisolone, and the triple group, respectively. Similar additive efficacy of the triple therapy was noted in the mean change of the total Larsen score, as well as the mean change in HAQ.

3.4.4.7 CAMERA

In the CAMERA study a total of 299 early RA patients were randomized to intensive care with monthly visits or to routine care with visits every 3 months (Verstappen et al. 2007). The initial treatment in both groups was MTX 7.5mg/week, and this was increased and further altered to parenteral administration and addition of CyA or switch to other DMARDs in case of insufficient treatment response. In the intensive care group the clinical outcome measures were entered into a computer decision program which analyzed whether the predefined response criteria (> 20 % improvement compared to the previous visit and > 50% improvement from baseline) were met and whether the treatment needed to be intensified or not. Opposite to TICORA, to CIMESTRA, and to FIN-RACo the intraarticular and systemic glucocorticoids were deliberately avoided. The main outcome of this study was reaching at least one 3-month period of remission, and that succeeded for 50% of the intensive care patients and for 37% of the routine care patients. All clinical variables appeared similar by the end of 2 years, but during this

follow-up the areas under curve were lower in the intensive care group. After 5 years the groups did not differ, the mean DAS28 values being 2.68 and 2.75 (Bakker et al. 2011). Good response according to EULAR criteria at 6 months predicted a good outcome at 5 years, irrespective of the original treatment allocation. Changing MTX to parenteral dosing increased the efficacy of the treatment whereas adding CyA did not (Bakker et al. 2010).

3.4.4.8 Swefot

In a Swedish multicenter study, 487 patients with early, DMARD-naïve RA were first all treated with MTX monotherapy, then assessed at 3-4 months, when the 258 patients tolerating MTX, but not having reached low disease activity (DAS28<3.2) were included in the Swefot study and randomized to receive either an addition of SASP and HCQ or that of infliximab to MTX (van Vollenhoven et al. 2009). At 12 months, the primary outcome, EULAR good response, was reached by 25% of the MTX+SASP+HCQ treated patients, and by 39% of the MTX+infliximab treated patients. Of the 147 patients not included in the Swefot study and having reached low disease activity with initial MTX, DAS28 remission was reached by 60% after 1 year, and by 72% after 2 years (Rezaei et al. 2011). However, regardless of the clinical outcome, 61% of the patients still progressed radiologically, at baseline 52% of the patients had had radiographic damage, while at 2 years 80% did so. Still, the progression of damage was moderate.

4. Treatment recommendations

4.1 Finnish Current Care guideline

According to the national Finnish guideline, early and aggressive application of DMARDs is essential for a positive treatment result in RA (Current Care Guideline 2009). Remission during the first year of treatment predicts permanent remission, milder joint damage and better functional ability. Methotrexate is recommended as the first DMARD, but as the authors of the Finnish guideline consider combination therapies to be more effective than single therapies, they recommend a combination of methotrexate, sulfasalazine, hydroxychloroquine and prednisolone to be initially used in active RA. For patients with an unsatisfactory response to DMARDs (including methotrexate and DMARD combinations), TNF blockers, or further, in non-responders, other biologics, should be used.

4.2 Other recommendations

Several national recommendations for the use of DMARDs exist. Of these, at least the United Kingdom (NICE 2009), the American (Saag et al. 2008), and the Canadian (Bykerk et al. 2011) versions deem initial combination treatment in active RA with poor prognostic factors (positive RF or ACPA, high disease activity or early radiographic changes) possible. However, the EULAR (Smolen et al. 2010a) recommendations suggest initial MTX monotherapy to all patients without contraindications, and if that fails and the patient has poor prognostic factors, adding a biologic. According to the EULAR recommendations, combining or switching traditional DMARDs is only the second option after MTX failure and reserved for patients without poor prognostic factors. Additionally, a so-called Treat to Target initiative has been published underlining the importance of aiming at sustained remission or low disease activity (Smolen et al. 2010b).

5. Realisation of medical treatment in early RA in clinical practice

5.1 Specialist opinions

Different methods can be utilized to assess the use of DMARDs. Interviewing rheumatologists is an accessible option. However, interviewed physicians may report more idealistic treatment strategies than the ones they actually use, and, moreover, in such studies the respond rate is seldom high.

In 1998, before the era of biologics, Maetzel et al. (1998) sent a survey about treatment strategies in RA to all members of the Canadian Rheumatology Association and to a 10 % sample of the members of the American College of Rheumatology, 214 (81.3 %) and 214 (66.9 %) of whom responded and were still practicing rheumatologists, respectively. The authors queried the first and second treatment choices in hypothetical patient cases representing: aggressive DMARD-naïve RA (26 actively inflamed joints and 3 erosions), moderate DMARD-naïve RA (6 actively inflamed joints, no erosions), and aggressive RA failing MTX. The majority of Canadian rheumatologists preferred MTX (68.7 %) as the first DMARD and im. gold (50.0 %) as the second one in aggressive RA. If MTX failed, more than half of the rheumatologists would still have continued with a single DMARD, most often SASP (34.6 %), 16.4 % would have combined HCQ and 3.3 % HCQ and SASP to MTX. The US rheumatologists appeared somewhat more active; in aggressive RA 78.5 % of them chose MTX as the first option, 11.2 % would have combined HCQ and 4.7 % both HCQ to MTX already as the first treatment. In aggressive RA failing MTX, triple therapy was the most common option (21.5 %), otherwise the choices spread widely. In moderate RA 90.2 % chose a single agent, equally commonly MTX (38.8 %) and HCQ (39.3 %).

Mikuls and O'Dell (2000) carried out an interview study of 200 US rheumatologists in 1999 and compared the responses to those from similar questionnaires in 1995 and 1997. MTX was the most commonly used initial DMARD; in 1999, 64 % of the US rheumatologists chose it as first-line therapy (in 1995 50 %, and in 1997 53 % did the same). HCQ, SASP and injectable gold were other possible first-line DMARDs. Combination treatment was deemed as suitable initial therapy by 47 % of the rheumatologists.

Jobanputra et al. (2004) reported the results of a postal interview about the treatment of early RA to 460 UK rheumatologists, 331 of whom responded. As the first treatment, 46.5 % of them preferred MTX, 43.5 % SASP, and 5 % either of these two. Depending on the first choice, the most common option for the second DMARD was switching MTX to SASP or vice versa, or combining them to each other and, in some cases, adding HCQ. If these treatments would have failed, leflunomide was valued over intramuscular gold, and after them, anti-TNF agents.

Maravic and colleagues (2004) sent a questionnaire about the diagnosis and treatment of RA to French rheumatologists, 917 (37 %) of whom answered. As initial treatment, only 74% would have prescribed DMARDs, most often MTX (46 %).

Through a postal questionnaire sent to Dutch rheumatologists (response rate 50 %), van Tuyl and colleagues (2007) noted that even though the physicians admitted the evidence-based efficacy of the Cobra combination treatment, they found the combination too complex to be used in clinical practice and worried about the possible side effects of high dose prednisolone.

5.2 Cohort studies

5.2.1 Clinical cohorts

Kvalvik and co-workers (2001) reviewed retrospectively the treatment data of a cohort of 147 patients who had had their first visit to a Norwegian tertiary rheumatology centre in 1977 due to RA, up to 1992 or the patients' death. They found that at the time of the diagnosis, in 1977, DMARDs were given to 62% of the patients, mainly to those with a short symptom duration and severe RA. During follow-up, 54 % of the patients received DMARDs, which were administered only for a median of 29 months.

As a subgroup of a larger Austrian single-institute material, Aletaha and Smolen (2002) present the data of the initial treatment in 222 early RA patients treated between 1971 and 1999. The authors report that throughout this long observation time, antimalarials, SASP, MTX, parental gold, oral gold and combination DMARDs were given to 34.7 %, 28.4 %, 16.2 %, 11.3 %, 6.8 % and 1.8 %, respectively. Gold compounds and antimalarials were the leading DMARDs in the beginning, SASP and MTX replaced them towards the end of the of the study period.

Saraux et al. (2002) present data of 98 early RA patients from 8 French rheumatology departments in Brittany between 1995-97. Injectable gold (32 %) and HCQ (34 %) were the most common initial DMARDs; 14 % of the patients were not prescribed any DMARDs at their first visit with RA. After 2-4 years follow-up, at their last visit within the study, 23 %, 23 %, 21 %, and 18 % of the patients were on MTX, injectable gold, HCQ or no DMARDS, respectively. Only 3 % of the patients received DMARD combination treatment.

Sokka and Pincus (2002) reviewed retrospectively the initial treatment of 232 early RA patients diagnosed after 1998 in a private US clinic. Single MTX was the first DMARD in 81.5 % and HCQ in 6.5 % of the patients; 7.3 % were not prescribed DMARDs initially. All the patients were evaluated in clinic in 2001, and at that time, after a mean disease duration of 21 months, 56.0 % of the patients were on single MTX, 15.5 % were using combinations of traditional DMARDs and 9.4 % combinations including biological agents; 9.1 % were not on DMARDs. At the study visit, 59.9 % of the patients were taking prednisone with the median dose of 5mg; 87.0 % of the patients had used prednisone for over two weeks at some time during their RA treatment.

5.2.2 Population-based cohorts

5.2.2.1 Early RA

Carli and colleagues (2006) analysed data from a national Swedish Rheumatoid Arthritis Register, including 2584 early RA patients from 19 Swedish hospitals diagnosed between 1997-2001. During the study period the use of DMARDs increased, which was mainly explained by the increased use of methotrexate; in 1997 approximately 20 % of the patients received it, while in 2001 55 % did so. The use of other DMARDs remained quite stable, but the proportion of patients without DMARDs decreased from 32.2% to 14.9%. Approximately 40 % of the patients were using oral GCs with a median dose of 7.5-10 mg. Active treatments were more often used by doctors practicing in university and county hospitals than by those from district hospitals.

The Norfolk Arthritis Register (NOAR) in the UK assesses the long-term follow-up data of adult patients presenting with inflammatory polyarthritis, thus not necessarily RA. From this register, two cohorts of patients were assessed; the first

one included in 1990-94 and the latter one in 2000-2004. In the first cohort 44.6% of the patients were ever treated with DMARDs [median (IQR) treatment time 0 (0-47) months, MTX 20.3 %] during the first 5 years of follow-up, in the latter cohort 71.9 % of the patients received DMARDs [51 (0-60) months, MTX 55.2 %] (Scire et al. 2011).

5.2.2.2 Established RA

Berard and co-workers (2000) published data of 10 262 New Jersey RA patients registered in different beneficiaries between 1992-1995. When the prescription data of these patients during 1995 was analysed, only 13% of them were prescribed any DMARDs; 57 % were using NSAIDs and 23 % oral glucocorticoids.

Edwards et al. (2005) present the data from 34 364 RA patients registered in the UK national database between 1987-2002. Only 50% of the patients were prescribed any DMARD during the study period, most often SASP (46.3%) or MTX (31.4%), the use of the latter having increased 17-fold during the study period, while the use of intramuscular gold had decreased.

In an observational study of 5 864 RA beneficiary program patients, 65 years or older, from US, Pennsylvania, treated for RA between 1995 and 2004, Schmajuk and colleagues (2007) found that the use of DMARDs increased during follow-up; in 1996 24% and in 2003 43% of the patients received DMARDs (41% and 70% of those with at least 1 rheumatologist visit). Older patients were less likely to receive DMARDs than the younger ones.

In Germany, a national database (the National Database of the German Collaborative Arthritis Centres) has been established in 1993 to monitor the treatment and outcomes of patients with arthritis (Zink et al. 2001). In the most recent publication on this database including data from 38 723 RA patients with a

mean disease duration of approximately 10 years, Ziegler et al. (2010) reported that from 1997 to 2007 the proportion of patients using combination DMARDs increased from 7.5 % to 22.8 %, that of patients on a single DMARD decreased from 74.3 % to 61.8 %. Throughout the follow-up, the percentage of patients with no DMARDs varied between 12.7 % and 19.2 % without a clear trend, but the proportion of patients using only GCs increased from 4.9 % to 8.1 %. The use of MTX remained stable at a level of 52.2-57.5 %. In 2007, 16.2 % of the patients received biologics. During the same follow-up, the mean DAS28 decreased from 4.5 to 3.4 and the proportion of patients in DAS28 remission (<2.6) more than doubled from 13.7 % to 29.3 %, reflecting the better results achieved by the increasingly aggressive treatment policy.

Neovius and co-workers (2011a) published a study on the prevalence of RA in Sweden, as well as on the penetration of anti-rheumatic treatment in that population, based on data from 58 102 patients alive in 2008. They found that in 2001-2007, 62 % of the patients received DMARDs, 49 % GCs and 15 % biologics.

6. The effect of medical treatment on work disability in RA

6.1 Conventional DMARDs

In 1991, in a Scandinavian multi-centre study Borg et al. (1991) proved, that early RA patients treated double-blindly with auranofin (n=42) for 24 months had at the end of the study a higher probability of continuing to work than those treated with placebo (n=41), with 57 % and 37 % of the patients in auranofin and placebo groups having unchanged working ability and 31 % and 39 % retiring prematurely, respectively. In this study, risk factors for early retirement were blue-collar jobs,

higher age and increased disability, but even when these were taken into account, the initial treatment with auranofin had a protective effect.

Within the FIN-RACo trial, Puolakka and others (2004) compared the incidence of sick leaves and work disability during 5 years follow-up in the 162 early RA patients who had been available to work force at baseline. They found that the patients initially treated with the FIN-RACo strategy had an annual median of 12 days of sick leave while the respective figure in the patients treated with the SINGLE strategy was 30 days. The proportion of patients receiving a permanent disability pension by 5 years was 20 % and 29 % in the FIN-RACo and in the SINGLE groups, respectively. However, the sex, age and baseline unemployment status adjusted hazard ratio was not statistically significant [1.25 (95 % CI: 0.65 to 2.41)]. In a following study the authors evaluated the relation of the clinical outcome at 6 months and the subsequent work disability at 5 years and showed that regardless of the initial treatment strategy, none of the patients achieving remission at 6 months became work disabled during 5 years (Puolakka et al. 2005a). Of the patients having an ACR50, ACR20 or less than ACR20 response at 6 months, 23 %, 21 %, and 56 %, respectively, became permanently work disabled by 5 years. In a monetary analysis of the FIN-RACo material better improvement of disease activity was associated with less cost (Puolakka et al. 2006).

In the 2-year cost-utility analysis of the BeSt study the authors present amongst other outcome measures the mean worked hours per week. During both the first and the second year these hours were higher in the initial combination groups than in the sequential monotherapy or the step-up combination therapy groups, 12-14 hours/week and 8-11 hours/week, respectively (van den Hout et al. 2009). In this

respect, the initial combination treatment with either prednisolone or infliximab did not differ from each other.

6.2 Biologics

Despite the excellent clinical results achieved by biological DMARDs, their effect on working ability is still unclear and possibly depends on the timing of the treatment.

6.2.1 Established RA

In 1999, Yelin with colleagues (2003) carried out a telephone interview of 194 RA patients who were using etanercept as a part of a clinical study and of 185 RA patients belonging to an observational study cohort and not using etanercept. These patients had been employed at the time of the diagnosis of RA, which in the etanercept users had took place a mean 14 years and in the non-users 17 years earlier. At the time of the study, 71 % of the etanercept users and 55 % of the non-users were employed and the authors found the difference significant even when adjusted for RA duration and severity, demographics, other health status, occupation and industry.

Within the large aforementioned US cohort (Allaire et al. 2008a), the same authors compared the risk of work disability between two subgroups; 1986 anti-TNF-treated patients and 1900 never-anti-TNF-treated patients, all of whom had been employed at disease onset and completed the required follow-up (Wolfe et al. 2007a). The authors noted that anti-TNF therapy in fact increased the risk of both self-reported and Social Security compensated work disability; when all covariates (demographics, comorbidities, disease severity, treatments) were included in the model, the difference remained statistically significant for self reported but not for Social Security compensated work disability. Further, from the same observational

US cohort, Allaire and co-workers (2008b) studied longitudinally the efficacy of TNF-inhibitors on work disability during 18 months of follow-up, and did not find any protective effect in a cohort of 953 RA patients. However, in a subanalysis, disease duration played a role so that patients with shorter (< 11 years) disease course benefited of TNF-inhibitors (OR 0.5 [0.2-0.9]) while patients with longer disease duration (> 11 years) did not (OR 1.6 [0.9-3.6]).

Halpern et al. (2009) followed up for 24 months 158 multinational RA patients receiving adalimumab as a part of an extension study of six prior clinical studies and 180 Norwegian register-based RA patients receiving traditional DMARD treatment, who would have fulfilled the inclusion criteria for the abovementioned adalimumab studies. All of these patients had been employed at baseline, while the authors report that at one year 117/158 (74 %) and 62/180 (34 %), and at two years 108/158 (68 %) and 36/180 (20 %) of the adalimumab and of the DMARD treated patients, respectively, would have continued working. However, these results are in great contrast with a figure from the same article, according to which the corresponding percentages were approximately 90 % and 75 % at one year, and 87 % and 67 % at two years. Whatever the figures the authors base their analysis on, they conclude that the patients receiving adalimumab had a decreased the risk of becoming work disabled (HR 0.36) and worked approximately seven months longer than non-anti-TNF treated patients.

Augustsson and co-authors (2010) describe a Swedish cohort of 594 patients treated with TNF-inhibitors and followed up for five years. At the beginning of the treatment the patients had a mean disease duration of 9.4 years and were all available to labour force. During follow-up, the weekly working hours increased by up to a mean of seven hours, especially in patients being able to continue treatment

with the same TNF-inhibitor. No figures on the incidence of permanent work disability were given and the study included no control group. However, it could well be hypothesized that in patients with severe enough RA to claim treatment with biologics, the natural prognosis of working ability without treatment would rather be deterioration than improvement.

Verstappen et al. (2010) present the British Society for Rheumatology Biologics Register data of 3291 RA patients treated with infliximab, etanercept or adalimumab and of 379 RA patients with active disease and treated with DMARDs between 2001-2005. The mean RA duration was 13 years in the anti-TNF-treated patients and 8 years in the DMARD-treated cohort. The working status of the patients was elucidated at baseline when already 49 % of the anti-TNF-treated patients and 36 % of the DMARD-treated patients were work disabled. After three years of treatment the incidence of new work disability was 9 % and 5 % in the anti-TNF- and DMARD-treated RA cohorts, respectively. The anti-TNF-treated patients who had reaching remission by six months after the induction of treatment had a reduced risk of consequent work disability; in others anti-TNF treatment did not appear to prevent loss of work ability. Elevated HAQ and manual job were risk factors for new work disability.

6.2.2 Early RA

In a clinical study setting, Smolen et al. (2006) analysed employment and employability data of 500 patients with a RA duration of less than 3 years and randomized to receive either infliximab or placebo infusions together with MTX and followed up for 54 weeks. The actual employment rate did not differ between the groups, the net employment loss was 1.3 % in the placebo group and 0.5 % in the infliximab group. However, fewer patients lost workdays and higher proportion

maintained their subjective employability in the infliximab group than in the placebo group.

Bejarano et al. (2008) randomised in 2003-04 a total of 148 employed, MTX-naïve, early RA patients to receive treatment with either MTX or with MTX plus adalimumab and followed them up for 56 weeks The primary end point was actual or imminent work loss after 16 weeks, which did not differ statistically significantly between the groups. However, presumably due to the early treatment failure in the MTX group, during the total follow-up, fewer patients in the MTX plus adalimumab group experienced actual or imminent job loss than in the MTX group, 19 % and 40 %, respectively. Imminent job loss was defined as a failure to achieve an ACR20 response and either deteriorating or persistently high scores in a specific questionnaire predicting a high risk of work disability; actual job loss was rare in either group (data not shown in the article).

AIMS OF THE STUDY

1. To compare the long-term effects of initial combination DMARD strategy starting with methotrexate, sulfasalazine, hydroxychloroquine, and low dose prednisolone to single DMARD strategy starting with sulfasalazine, with or without prednisolone on clinical outcomes in patients with early RA.

2. To compare the long-term effects of initial combination DMARD strategy starting with methotrexate, sulfasalazine, hydroxychloroquine, and low dose prednisolone to single DMARD strategy starting with sulfasalazine, with or without prednisolone on radiographic damage in patients with early RA.

3. To study the initial treatment of early RA in the whole Finnish population and to estimate how it adheres to the contemporary recommendations.

4. To study how work disability in early RA patients has changed during this millennium in Finland.

MATERIALS AND METHODS

7. The FIN-RACo 11-year follow-up studies (I and II)

7.1 Patients

Between April 1993 and May 1995, in a multicenter setting, 199 DMARD-naïve patients with a recent onset RA (symptom duration <2 years; median 6 months) were admitted to this open, parallel-group and randomized study comparing the efficacy and tolerability of two treatment strategies (4). The patients could be included in the study if they fulfilled the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria for RA (13), were aged 18–65 years, had a duration of symptoms of less than 2 years, and had an active disease, with at least three swollen joints and at least 3 of the following 4 features: either an erythrocyte sedimentation rate (ESR) ≥28 mm/hour or a C-reactive protein (CRP) level >19 mg/l, morning stiffness ≥29 minutes in duration, >5 swollen joints, and >10 tender joints.

7.2 Study design

7.2.1 Study design during the first 2 years

The FIN-RACo strategy included an initial combination of three DMARDs and was started with methotrexate 7.5 mg/week, sulfasalazine 500 mg twice daily, and hydroxychloroquine 300 mg/day, with prednisolone 5 mg/day, but the dosages could be adjusted to achieve remission. The highest dosages allowed were 15 mg/week for methotrexate, 2 gm/day for sulfasalazine, and 10 mg/day for prednisolone. If, for any reason, any of these drugs had to be discontinued, it was replaced with a different DMARD so that constantly a combination of three DMARDs was used. The SINGLE strategy was initiated according to the

"sawtooth" strategy, using sulfasalazine (2 g/day) as the first drug for all patients. The dosage could be increased to 3 g/day, and the simultaneous use of prednisolone up to 10 mg/day was allowed. If the clinical response was insufficient or if an adverse event occurred, sulfasalazine was replaced with methotrexate, and if needed, further with a different single DMARD. In all patients the treatment was targeted toward remission and thus intra-articular glucocorticoid injections into inflamed joints were allowed and even exhorted for.

7.2.2 Study design after 2 years

After 2 years, the use of DMARDs became unrestricted. However, in both groups the treatment was still aimed at maintaining or achieving remission. Therefore, regardless of the original randomization group, patients who had an insufficient response could be treated liberally with increased dosages of DMARDs and with DMARD combinations as tolerated and clinically indicated. Once available to market, biological DMARDs could be used. On the other hand, if a patient was in long-term remission, the protocol required drug dosages to be reduced and eventually tapered off, beginning with prednisolone. If it could be discontinued without losing remission, one DMARD per year could gradually be tapered down. If RA was reactivated, the last medication and dosage at which remission was maintained was reinstituted. As a consequence, depending on the clinical situation, the drug therapies of the study patients could vary from no DMARDs or prednisolone to a combination of DMARDs as well as to biological agents.

7.3 Clinical assessments

The treating rheumatologist performed all clinical assessments. During the first 2 years the study visits occurred every 1-3 months, between 2-5 years every 6 months and after that once a year. All patients who had participated in the 5-year follow-up

survey were invited to participate in the 11-year follow-up visit even if they had not participated otherwise after 5 years and, on the other hand, only patients who had participated at 5 years were included in the 11-year analysis.

Outcome measures included the patient's self-report of physical functioning and assessment of RA clinical activity, including all the measures required to determine the frequency of remissions. The medications used by the patients were recorded at each study visit. DMARD strategies used between year 2 and year 11 were carefully elucidated based on the patient's self report and his or her medical records. Serious adverse events, including death, any life-threatening event, malignant disorders, and any event that necessitated hospital admission, among the patients participating in the 11-year follow-up were recorded. The vital status of all patients who had entered the study was inquired from the Local Register Office. Death certificates for all deceased patients were obtained from the office of Statistics Finland. Comorbidities and their duration were inquired from the patient as well as from the medical records. Functional capacity was assessed with the Health Assessment Questionnaire (HAQ) (Fries et al. 1980). Clinical activity of RA was assessed with the Disease Activity Score 28-joint assessment (DAS28) (Prevoo et al. 1995).

Modified Minimal Disease Activity (MDA) was assessed to be present, if the patient had no swollen joints, no tender joints, and an ESR ≤10 mm/hour or fulfilled of at least 5 of the following 7 criteria: swollen joint count ≤1 (range 0–52), tender joint count ≤1 (range 0–52), HAQ score ≤0.5 (range 0–3), visual analog scale (VAS; 0–100-mm scale) score for pain ≤20, for the patient's global assessment of disease activity ≤20, and for the physician's global assessment of disease activity ≤15, and an ESR ≤20 mm/hour. In this study a 52-joint count of tender and swollen joints

was used, instead of the 28-joint count used in the original analysis (Wolfe et al. 2007b), which made these modified criteria more stringent.

Also the definition of remission used in this study was very strict; it included the fulfilment of all the other 5 ACR criteria (Pinals et al. 1981), when fatigue and duration of remission criteria were excluded. Thus, a patient in remission could not have any tender or painful joints, no swollen joints or tendon sheaths, no elevation of the ESR (normal <30 mm/hour in women and <20 mm/hour in men), nor a duration of morning stiffness of >15 minutes. Remission according to the DAS28 was defined as score of <2.6.

7.4 Radiological assessment

The hands and feet of all patients were radiographed at baseline, at 2, 5 and at 11 years. Radiographs of hip, knee, elbow and shoulder joints of the patients were taken at 11 years in 13 study centers; in 2 study centers only clinically symptomatic large joints were radiographed. Total joint replacements were assessed from the radiographs as well as from the patients' medical records. The same experienced radiologist (LL), who was blinded to the clinical data but aware of the order of the radiographs, assessed the radiographs and scored the radiographs of hands and feet according to the method of Larsen et al. (Larsen et al. 1977) with the range from 0 to 200. The large joints were also scored according to the method of Larsen (Larsen et al. 1977) and a score of ≥ 2 was considered indicating erosive disease.

7.5 Ethical considerations

The study was performed according to the principles of the Declaration of Helsinki. The protocol was approved by the national health authorities and ethics committees of all 18 participating hospitals. All patients gave written informed consent.

7.6 Statistical methods

Results are presented as the mean ± standard deviation (SD), the median with the interquartile range (IQR), or counts with percentages. The 95% confidence intervals (95% CIs) are given for the most important outcomes. Statistical comparison between groups was performed with the *t*-test, permutation test, chi-square test, or Fisher's exact test, as appropriate. Repeated measures for continuous and binary outcomes were analyzed using generalized estimating equation (GEE) models with the exchangeable correlation structure. GEE models do not require complete data and can be fit even when individuals do not have observations at all time points. The Cox proportional hazards model was used to estimate the adjusted risk of death between groups. The underlying proportional hazards assumption was tested by computing the Schoenfeld residuals for each of the covariates in the final model and plotting them against the length of survival. The standardized mortality ratio (i.e., the ratio of observed to expected deaths) was calculated using the subject-years method with 95% CIs, assuming a Poisson distribution. Probabilities of survival in an age- and sex-matched sample of the general population were calculated from data from the Official Statistics of Finland.

The 95 per cent confidence intervals (95 % CI) for Larsen score are obtained by bias-corrected bootstrapping due to the skewed distribution. The difference in crude change in Larsen score between the groups was tested by a permutation test. A random coefficient model with bootstrapped standard errors was adapted to analyze the progression of Larsen score during 11 years and to compare the groups in time. An ordered logistic regression analysis was used to estimate the prediction of achieving radiologic progression. The adjusted risk ratio (RR) between the groups for having no erosive changes in large joints was estimated by a generalized linear

model (log link) with presence of erosion in hands or feet at baseline as covariate. A time-to-event analysis based on the product limit estimate of the cumulative "survival" function (Kaplan- Meier) was used in order to describe the time to event. A log-rank test was used to identify any survival difference between the groups.

8. The Finnish early RA register studies (III and IV)

8.1 Background

In Finland, the entire population is covered by general sickness insurance, and all permanent residents are issued a personal health insurance card. The Social Insurance Institution (SII) generally reimburses the costs of medicines prescribed by a doctor and intended for the treatment of an illness. The basic reimbursement rate is 42% of the price of the medicine, but patients with certain severe and chronic diseases are entitled to a special reimbursement of medications if their condition meets predefined criteria. Thus, the patients with chronic inflammatory rheumatic disorders can be granted the special reimbursement of 72% for antirheumatic drugs. To establish entitlement, the patient must submit to the SII a medical certificate issued by a specialist or based on examinations performed by a specialist-level health care unit. The medical certificate must include information on proper diagnostic procedures, an ICD-10 diagnosis, and a treatment plan according to a good clinical practice. An insurance physician of SII reviews the certificates before the special reimbursement can be granted. The administrative process usually takes a couple of weeks. Practically all Finnish patients with antirheumatic medications receive the reimbursement decision as it is economically in the patients' interest and if the reimbursement decision does not exist, the pharmacists generally encourages the patient to request it. At one transaction up to three months' supply of medicines can be reimbursed.

Finland has two, complementary, statutory pension systems; the national pensions and earnings-related pensions. National pensions, awarded and paid by the SII, offer a basic income for persons who are entitled only to a very small earnings-related pension or to none at all. Earnings-related pension rights accumulate through employment and self-employment. There are several earnings-related pension providers all of whom belong to the Finnish Centre for Pensions.

If unable to work, 16-67 year-old persons with long-term illnesses will first be paid a sickness allowance for up to 150 working days. After that, 16-64 year old persons who have lived in Finland for at least 3 years and who have an illness, injury or defect that prevents them from earning a reasonable living, stated by a doctor's certificate, can apply either for a temporary rehabilitation allowance or a permanent disability pension. Permanent disability pensions are usually granted, at the earliest, after one year of sick leave or rehabilitation allowance. Persons over 60 years may get a disability pension on somewhat easier terms. In case of application for both a national pension and an earnings-related pension on account of disability for work, SII and the responsible pension provider consult each other before issuing a decision. The SII and the Finnish Centre for Pensions maintain a register on sick leaves, rehabilitation allowances and permanent disability pension.

8.2 Patient cohort

The SII maintains a nationwide register of all medicine reimbursement decisions. From that register the data were gathered from 1.1.2000 to 31.12.2007, including information on sex, date of birth, and the date of reimbursement decision (index day) of patients who, for the first time in their life, had been granted a special reimbursement of medications for rheumatoid factor (RF) -positive (ICD-10

diagnosis M05) or RF-negative RA (M06). According to the index day the patients were divided into 2-year cohorts (2000-01, 2002-03, 2004-05, 2006-07).

For the work disability analysis, similar data were separately collected for 18-64 year-old patients who were available for labour force at the index day.

8.3 Medications

The SII maintains a prescription register on the drugs purchased from pharmacies and reimbursed according to the basic or the special rate. In this register, drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification (WHO 2009). The register includes the date of purchase and the amount of the drug. From this register, we collected data on the antirheumatic drugs purchased by the 4 patient cohorts for 31 days before the index day (to include medication possibly purchased before the reimbursement decision) and for 31 days, for 91 days, and for one year after the index day. Since prednisolone 5 mg tablets were not reimbursed in Finland between 1.1.2006 and 30.11.2007 the purchase of glucocorticoids was assessed only between years 2000 and 2005. Also, the intravenous drugs given and reimbursed by hospitals and outpatient clinics are not registered by the SII. Consequently, our study does not include infliximab or other infusion-based biological therapies. In addition to the distinct first-month and first-year DMARDs used by the patient cohorts, we investigated the early drug treatment strategies up to 3 months from the index day - no DMARD, single conventional DMARD, combination of conventional DMARDs, or treatment including TNF-inhibitors – and the change in strategy over time.

For the patients available to work force at the index day we collected data on the antirheumatic drugs purchased by the 4 patient cohorts from 31 days before (to include medication possibly purchased before the reimbursement decision) up to 91

days after the index day. We studied the early drug treatment strategies up to 3 months from the index day: no DMARD, single non-methotrexate (MTX) DMARD, single MTX, combination of DMARDs not including MTX, or combination of DMARDs including MTX. The initiation of adalimumab or etanercept during the first 3 months as well as during any time throughout the follow-up was elucidated.

8.4 Work disability

From the registers of the SII and of the Finnish Centre for Pensions data were collected for the patients in each cohort (2000-01, 2002-03, 2004-05, 2006-07) available to work force at the index day. The annual work disability (WD) days were analyzed, including all periods of sickness allowance, temporary rehabilitation allowance, partial disability pensions (the number of the days divided by 2), and of permanent disability pension from 31 days before the index day up to the end of follow-up, 31 Dec 2008. However, sick leaves shorter than or equal to 10 days are not compensated by the SII, and could thus not be assessed. The mean annual WD days per patient years for any reason were counted for each cohort. In this analysis also the patients already on partial pensions on index date were included, and the number of their WD days was divided by 2. During the same period permanent disability pensions, as well as long-term rehabilitation allowances still continuing at the end of our follow-up, were elucidated, including WD pensions for any reason and those exclusively due to RA. The follow up of the patients ended when they retired because of another reasons than RA, became 65 years old, or died, whichever the first. From the same institutes the incidence data of premature work disability pensions of all 18-64 year-old Finnish citizens were received.

8.5 Ethical considerations

There was no legal requirement for approval by an ethics committee, since only unidentifiable register data were used and patients were not contacted.

8.6 Statistical methods

When analyzing the medications used, the statistical comparisons between groups were made by using analysis of variance (ANOVA) and chi-square test. Statistical significance for hypotheses of linearity was evaluated by Cochran-Armitage test. In the work disability analysis the results are expressed as means with standard deviation (SD) and as medians with interquartile range (IQR). Statistical significance for hypotheses of linearity was evaluated by analysis of variance (ANOVA), Cochran-Armitage test. The 95% confidence intervals for annual WD days were obtained by bias-corrected bootstrapping and the linearity across year-cohorts was tested by bootstrap type analysis of covariance with an appropriate contrast. The cumulative incidence of continuous WD was estimated and illustrated by Kaplan-Meier method. In order to adjust for confounding factors, the differences between the groups and the hypothesis of linearity were tested by using Cox's regression models with a contrast, when appropriate. Cox's multivariate regression model was also used to analyse factors associated to continuous WD. The underlying proportional hazards assumption was tested by computing the Schoenfeld residuals for each of the covariates in the final model and plotting them against the length of survival. The patients with RA and the population at risk were stratified by gender and age (in 5 year categories), and incidence rates with 95% confidence intervals (CI) were calculated. The ratio between observed and expected numbers, Standardized Incidence Ratio (SIR), was calculated with 95% confidence

intervals, assuming a Poisson distribution; significance for hypotheses of linearity was evaluated by Poisson regression models.

SUMMARY OF THE RESULTS

9. Long term outcomes of the FIN-RACo strategy

9.1 General results

9.1.1 Demographics and baseline clinical characteristics

Figure 1 presents a flow chart of the study patients. One-hundred ninety-nine patients were originally randomized to the study and 195 of these started the treatment, 97 in the FIN-RACo group and 98 in the SINGLE group. Two patients in both groups withdrew consent before receiving the first dosage of study medication. The 2-year follow-up was completed by 178 patients and the 5-year follow-up by 160 patients. After the 5-year visit, 6 patients in the FIN-RACo group and 7 in the SINGLE group had either changed residence, were reluctant to continue the follow-up, or had been enrolled at a center that did not participate in the study after 5 years (Figure 1) and therefore did not participate at the 11-year visit. During the entire 11-year follow-up period, 6 patients in the FIN-RACo group and 9 in the SINGLE group had died. Thus, a total of 138 patients were assessed at the 11-year visit, 68 in the FIN-RACo group and 70 in the SINGLE group (**I**). Radiographs of hands and feet were available at baseline and at 11 years in 65 cases in each group (**II**).

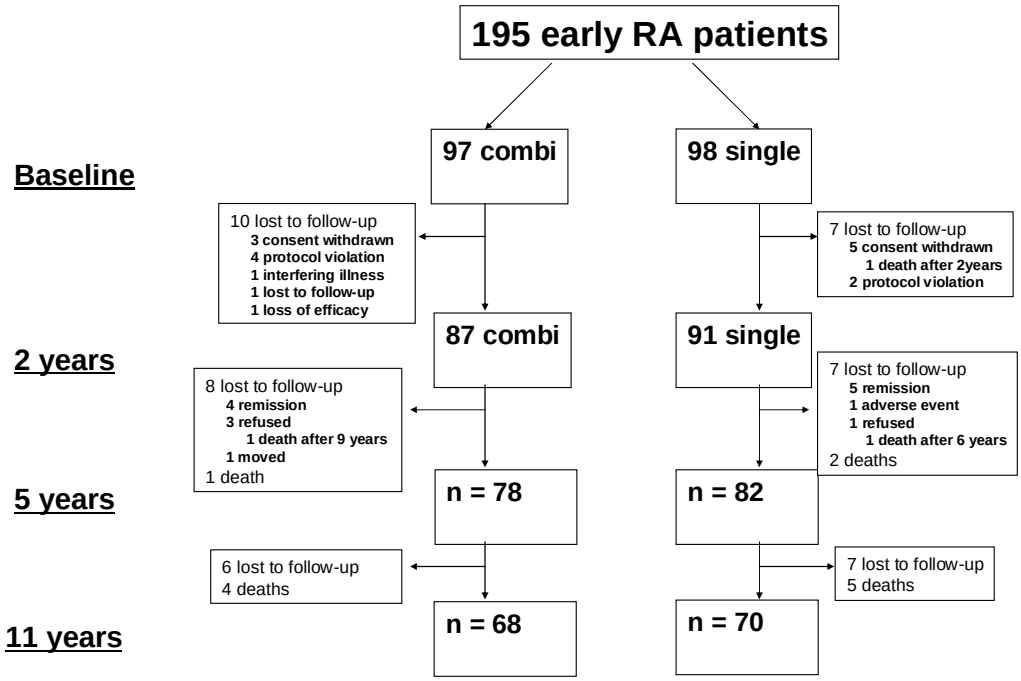

Figure 1. Flow-chart of the patients participating in the FIN-RACo study during 11 years (**I**)

The baseline demographic and clinical characteristics of the patients did not differ significantly between the groups (Table 12). The participants and the dropouts in both study arms had similar clinical and demographic data at baseline and at 2 years, as well as did the dropouts of both study groups (data not shown). Nevertheless, a trend towards a higher mean (range) Larsen score at baseline was found in the SINGLE group compared to the FIN-RACo group: 5 (0-30) vs. 3 (0-25) ($p = 0.069$). Furthermore, the dropout cases in the FIN-RACo group had a higher mean ± SD Larsen score at baseline than the completers: 6 ± 9 vs. 3 ± 6 ($p = 0.037$). In the SINGLE group the baseline Larsen scores did not differ between the dropouts and the completers: 3 ± 5 vs. 5 ± 7 ($P = 0.22$).

Table 12. Baseline demographics and clinical characteristics of the original FIN-RACo and SINGLE patients participating at the 11-year follow-up (**I**)

Characteristic	Randomization group for the 2 initial years		*P*
	FIN-RACo (n = 68)	SINGLE (n = 70)	
Demographic Data at Baseline			
Age (years), mean ± SD years	46 ± 9	47 ± 11	0.41
Female, no. (%)	42 (62)	48 (69)	0.40
Rheumatoid factor present (%)	49 (72)	46 (66)	0.42
Duration of disease (months), median (IQR)	6 (4–9)	7 (4–12)	0.23
Measures of Disease Activity at Baseline			
Number of swollen joints, median (IQR)	13 (9–16)	13 (10–16)	0.84
Number of tender joints, median (IQR)	16 (12–22)	16 (13–24)	0.76
Erythrocyte sedimentation rate (mm/h), median (IQR)	27 (16–48)	33 (22–54)	0.087
Patient's global assessment (VAS, mm), median (IQR)	48 (29–65)	47 (30–61)	0.84
Pain (VAS, mm), median (IQR)	47 (27–63)	48 (26–61)	0.64
Physician's global assessment (VAS, mm), median (IQR)	38 (31–54)	43 (30–59)	0.81
DAS28, mean ± SD	5.39 ± 0.86	5.65 ± 1.13	0.13
Physical function (HAQ, range 0-3) , mean ± SD	0.82 ± 0.53	0.90 ± 0.63	0.43

SD = standard deviation; IQR= Interquartile range; VAS = visual analog scale; DAS28 = disease activity score assessing 28 joints; HAQ = health assessment questionnare

9.1.2 Treatment strategies after 2 years

The treatment strategies became unrestricted after 2 years, but were still targeting remission. At 11 years, methotrexate was the most commonly used DMARD, followed by hydroxychloroquine and sulfasalazine (Table 13). At the 11-year visit, various combinations of synthetic DMARDs were used by 32 (47%) of the FIN-RACo group and 32 (46%) of the SINGLE group patients. Fifteen (22%) and 23 (33%) of the patients in the FIN-RACo therapy and SINGLE groups were using a single DMARD, respectively, and 13 (19%) and 10 (14%) patients no DMARDs at all, respectively.

Table 13. Antirheumatic medications used by the original FIN-RACo and SINGLE groups at the 11-year visit.

Medications at the 11-year visit, n (%)	Randomization group for the first 2 years	
	FIN-RACo (n = 68)	SINGLE (n = 70)
Methotrexate	39 (57)	42 (60)
Hydroxychloroquine	36 (53)	26 (37)
Sulfasalazine	29 (43)	23 (33)
Leflunomide	2 (3)	7 (10)
Cyclosporine	1 (2)	5 (7)
Aurothiomalate	2 (3)	4 (6)
Auranofin	1 (2)	2 (3)
Podofyllotoxin (CPH 82)	1 (2)	2 (3)
Azathioprine	0 (0)	1 (1)
TNF-inhibitors	8 (12)	4 (6)
Rituximab	0 (0)	1 (1)
Prednisolone	22 (32)	33 (47)

A biological agent was used by 8 (12%) of the patients in the original FIN-RACo group (in 3 patients with a DMARD-combination of and in 5 with a single DMARD). In the original SINGLE group, 5 (7%) of the patients were using a biological agent (in 2 patients with a DMARD-combination of and in 3 with a single DMARD). At some time between the 2-year and the 11-year visits, a combination-DMARD strategy had been used by 62 (91%) of the patients in the original FIN-RACo group and by 56 (80%) of the patients in the original SINGLE group ($p = 0.062$). The respective figures for single-DMARD strategy were 39 (59%) of those in the original FIN-RACo group and 56 (80%) of those in the original SINGLE group.

Twenty-two (33%) of the patients in the FIN-RACo group and 27 (39%) of those in the SINGLE group had been able to discontinue all DMARDs, at least

temporarily, during the follow-up period from year 2 to year 11. The median percentage of time receiving the combination-DMARD strategy between year 2 and year 11 was 79% (IQR 43–100) in the original FIN-RACo group and 54% (IQR 3–94) in the original SINGLE group (p = 0.0043). The respective median percentages for receiving the single-DMARD strategy were 5% (IQR 0–30) and 35% (IQR 3–67) (p < 0.001), and the respective median percentages for receiving the no-DMARD strategy were 0% (IQR 0–6) and 0% (IQR 0–8) (p not significant).

9.2 Clinical outcomes (I)

9.2.1 ACR Remissions

At 11 years the strict ACR remission criteria were met by 37% (95% CI: 26 to 49) of the FIN-RACo group and by 19% (95% CI: 11 to 29) of the SINGLE group (p = 0.017) (Figure 2) with a significant age-, sex-, and baseline DAS28–adjusted treatment effect over time (*P* = 0.0015). When analysing the ACR remission rates at 2, 5, and 11 years, 13% of the patients in the FIN-RACo group were in remission at all 3 time points, 54% at 1–2 time points, and 32% at no time points. In the SINGLE group, these percentages were 3%, 37%, and 60%, respectively. The difference between the groups was significant (p = 0.006, adjusted for age, sex, and baseline DAS28).

Of the 68 patients in the FIN-RACo group participating at 11 years, 18 (26.4 %) had reached remission at 6 months, and of those 13 (72.2 %) were in remission also at 11 years. In the SINGLE group the respective proportions were 7 out of 70 (10.0 %) and 2 out of 7 (28.6 %) (Figure 3). Thus, remission at 6 months predicted remission at 11 years in the FIN-RACo group [RR 3.08 (95 % CI: 1.85–5.14)

(p<0.001, adjusted for age and rheumatoid factor presence)], but not in the SINGLE group [RR 1.88 (95 % CI: 0.52–6.73) (p = 0.34)].

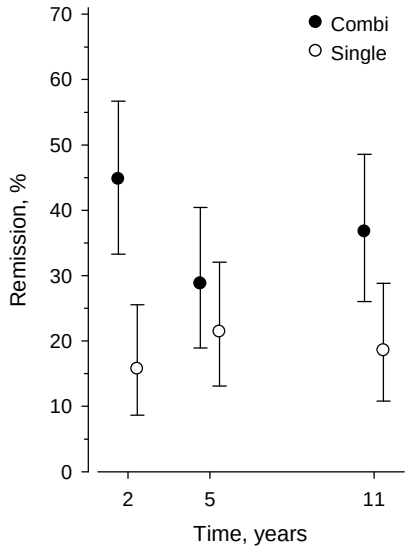

Figure 2. The percentage of patients in strict ACR-remission at the 2, 5, and 11 year visits. The values are presented as means with 95% confidence intervals (**I**).

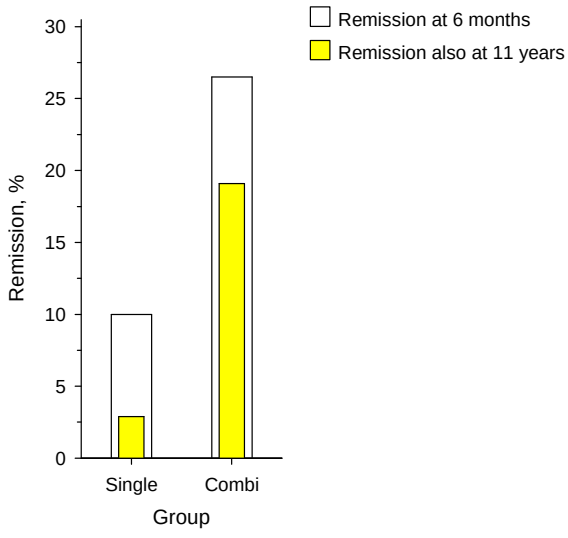

Figure 3. The proportions of patients in remission at 6 months and at 11 years in the two original randomization groups.

9.2.2 Disease activity according to the modified MDA and the DAS28

The clinical characteristics of the patients at the 11-year follow-up visit are shown in Table 14. Clinical disease activity was similarly low in both treatment groups, only the physician's global assessment of disease activity favoured the FIN-RACo group. Yet, at 11 years the modified MDA criteria were met more often by the patients in the original FIN-RACo group [63% (95% CI: 51 to 77)] than by those in the original SINGLE group [43% (95% CI: 32 to 55)] (p = 0.016).

Table 14. Measures of disease activity at the 11-year visit in the patients participating in the FIN-RACo study (**I**)

Measures of Disease Activity at 11 years	Randomization group for the 2 initial years		*P*
	FIN-RACo (n = 68)	SINGLE (n = 70)	
DAS28, mean (SD)	2.48 ± 1.22	2.73 ± 1.23	0.23
Erythrocyte sedimentation rate (mm/h), median (IQR)	10 (6–21)	13 (6–20)	0.61
Number of swollen joints, median (IQR)	0 (0–3)	2 (0–4)	0.10
Number of tender joints, median (IQR)	1 (0–5)	2 (0–5)	0.25
Patient's global assessment (VAS, mm), median (IQR)	16 (3–35)	19 (5–36)	0.26
Pain (VAS, mm), median (IQR)	15 (3–30)	16 (5–34)	0.35
Physician's global assessment (VAS, mm), median (IQR)	5 (1–14)	12 (3–19)	0.016
Physical function (HAQ, range 0-3), mean ± SD	0.34 ± 0.54	0.38 ± 0.58	0.88

DAS28 = disease activity score assessing 28 joints; HAQ = health assessment questionnare; IQR= Interquartile range; SD = standard deviation; VAS = visual analog scale;

At 2 years, the prevalence of the modified MDA had been 70 % (95% CI: 58 to 81%) in the FIN-RACo group and 50 % (95% CI: 38 to 62%) in the SINGLE group. Had the modified MDA been present at 2 years, it was also present at 11 years in 74 % (95 % CI: 60 to 86 %) of the FIN-RACo and in 51 % (95 % CI: 34 to 69 %) of

the SINGLE patients (p = 0.024, adjusted for age, sex, and baseline DAS28). Had MDA not been present at 2 years, the respective numbers were 35 % (95 % CI: 15 to 59 %) and 34 % (95 % CI: 19 to 52 %) (p = 0.81) (Figure 4). In the FIN-RACo group the only predictive factor for MDA present at 11 years was MDA present at 2 years (p = 0.028), but not age, sex, RF, baseline DAS or duration of combination DMARD treatment after 2 years. None of these factors was statistically significant in the SINGLE group.

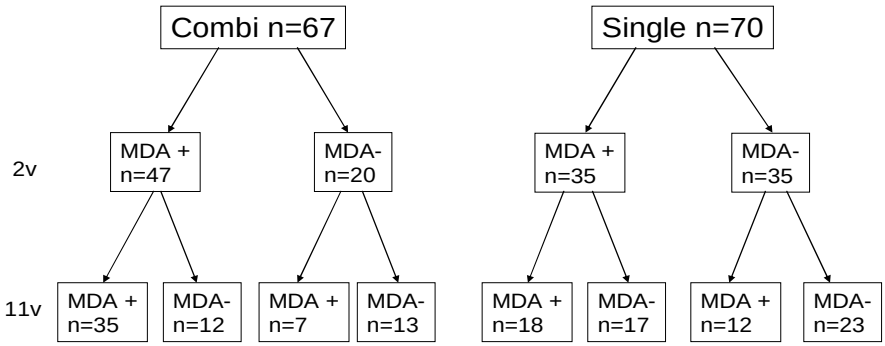

Figure 4. Number of patients in different original randomization groups reaching modified minimal disease activity at the 2 and 11-year visits

The mean DAS28 scores are shown in Figure 5. The treatment effect over time showed a significant advantage for the original FIN-RACo group as compared to the single group (p = 0.0022). At 2, 5, and 11 years, the mean DAS28 score in patients of the original FIN-RACo group was below the reported DAS28 remission limit (<2.6), while in those of the original SINGLE group the mean DAS28 scores remained in the area of low disease activity. DAS28 remission at 11 years was reached by 57% (95% CI: 45 to 69) of the FIN-RACo group and by 49% (95%: CI 37 to 60) of the SINGLE group (p = 0.30).

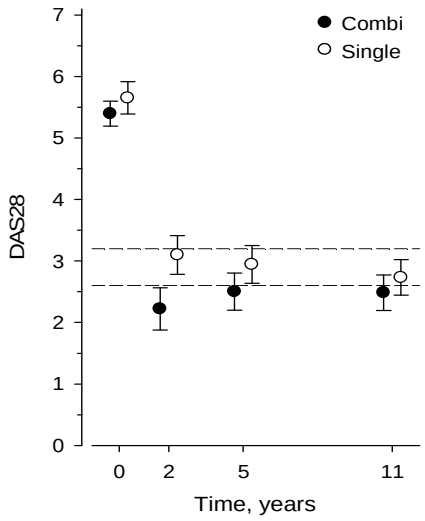

Figure 5. The mean DAS28 scores at different time points in the two original randomization groups. The values are presented as means with 95% confidence intervals (**I**)

9.2.3 Functional ability

The HAQ scores decreased from baseline to 2 years statistically significantly in both treatment groups ($P < 0.001$), with a mean decrease of –0.56 (95% CI: –0.70 to –0.42) in the FIN-RACo group and –0.61 (95% CI: –0.74 to –0.47) in the SINGLE group. The decrease was similar in both groups, thus the age-, sex-, and baseline DAS28–adjusted treatment effect over time was not significant (p = 0.90) (Figure 6). At 11 years, 56% of the patients of the FIN-RACo group and 43% of the SINGLE group had a HAQ score of 0 and HAQ scores >1 were present in only 10% and 9% of the patients, respectively (Figure 7).

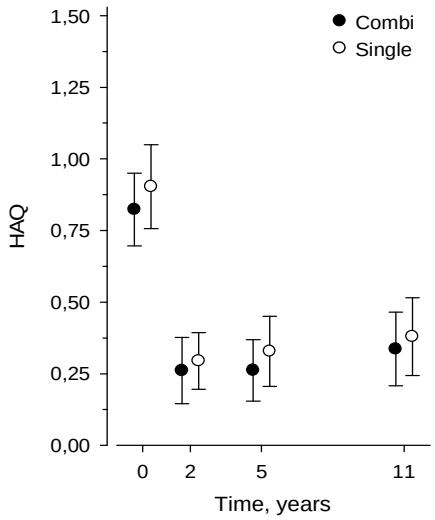

Figure 6. HAQ scores at different time points in the two original randomization groups. The values are presented as means with 95% confidence intervals (**I**)

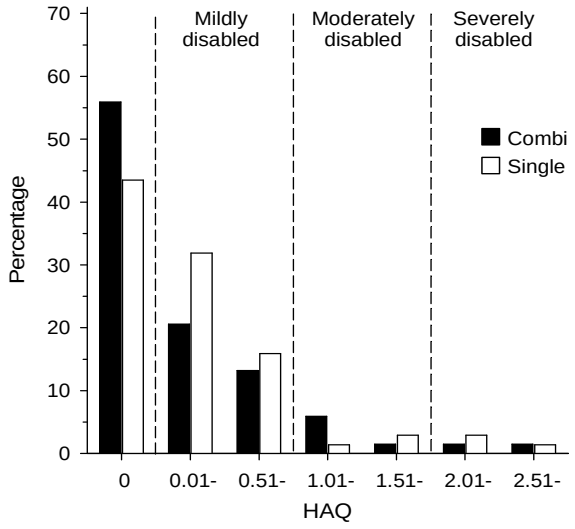

Figure 7. HAQ scores in different treatment groups at the 11-year visit (**I**)

9.3 Radiographic outcomes (II)

9.3.1 Small joints of hands and feet

The mean Larsen scores of hands and feet at baseline, and at 2, 5 and 11 years in both groups are shown in Figure 8. The crude mean change in Larsen score from baseline to 11 years was 17 (95% CI: 12 to 26) in the FIN-RACo group and 27 (95% CI: 22 to 33) in the SINGLE group ($p = 0.037$). When using all time points (0, 2, 5 and 11 years) and adjusting for Larsen score at baseline, the progression of Larsen score differed statistically significantly between the groups ($p = 0.021$, for time-by-group interaction-effect) with the FIN-RACo group having on average lower progression ($p < 0.001$, for group-effect).

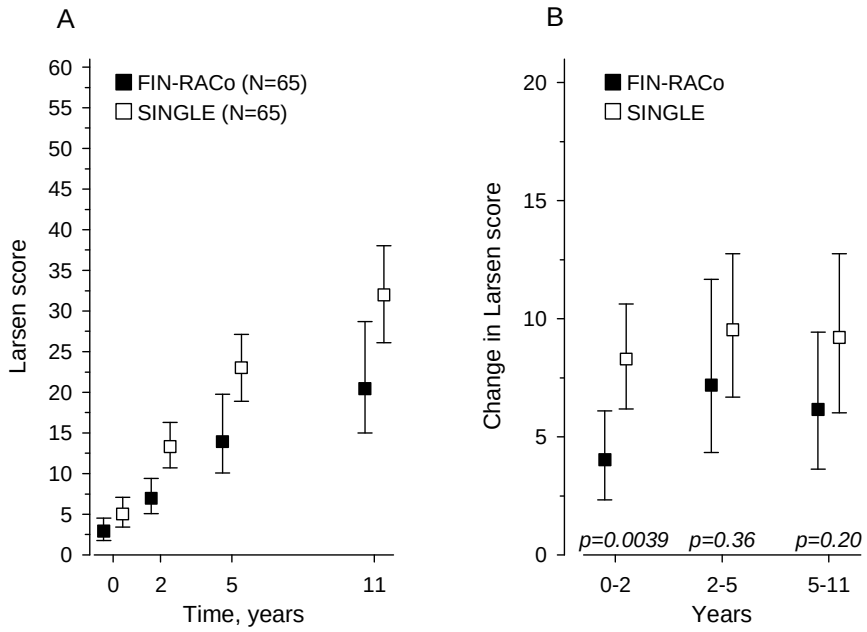

Figure 8. A. Mean Larsen score at different time points according to the original randomization group. **B.** The mean changes in Larsen score during years 0-2, 2-5 and 5-11 according to the initial treatment groups. The values are presented as means with 95% confidence intervals (**II**)

In a multivariate ordered logistic regression analysis the progression of joint damage in the small joints of hands and feet at 11 years was predicted by RF-positivity at baseline and by initial SINGLE strategy (Table 15).

Table 15. Multivariate ordered regression analysis of factors for radiographic damage in small joints after 11 years of RA (**II**)

Variable at baseline	Odds ratio (95% CI)	P-value
Female sex	1.74 (0.84 to 3.60)	0.13
Age, years	0.99 (0.96 to 1.02)	0.60
Disease duration before diagnosis, months	1.02 (0.94 to 1.10)	0.68
Rheumatoid factor positivity	3.17 (1.45 to 6.92)	0.004
Erythrocyte sedimentation rate	1.01 (0.99 to 1.02)	0.33
Larsen score	0.99 (0.94 to 1.05)	0.77
Initial randomization group		0.016
FIN-RACo	1.00 (reference)	
SINGLE	2.39 (1.78 to 4.84)	

In RA patients being in remission at 1 year the crude mean change from baseline to 11 years in Larsen score was 10 (95% CI: 6 to 16) as compared to 25 (95% CI: 21 to 31) in RA patients not being in remission at 1 year ($p = 0.001$) (Figure 9). When using all time points (0, 2, 5 and 11 years) and adjusting for Larsen score at baseline, the progression of Larsen score differed statistically significantly between the patients in remission and not in remission at 1 year ($p < 0.001$, for time-by-group interaction-effect) with the patients in remission at 1 year having on average lower progression ($p < 0.001$, for group-effect).

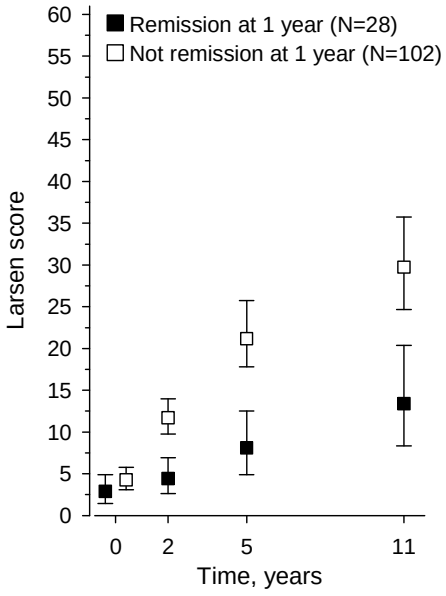

Figure 9. The mean Larsen score at different time points in patients in remission or not in remission at one year regardless of the original randomization group. The values are presented as means with 95% confidence intervals (**II**)

9.3.2 Large joints

At 11 years, 52 patients in the FIN-RACo and 54 in SINGLE groups had all their large joints radiographed. Respectively, 87% (95% CI: 74 to 94) and 72% (95% CI: 58 to 84) of these patients had no erosive changes in their large joints at 11 years [RR 1.22 (95% CI: 0.99 to 1.50)]. Damage to any large joint was present in 13% of the FIN-RACo and 28% of the SINGLE patients; the number of damaged large joints (Larsen score ≥ 2) did not differ between the groups (Table 16).

9.3.2.1 Need for joint replacement therapy

Four patients in the FIN-RACo and 5 in the SINGLE group had altogether 12 total joint replacements (6 knees and 6 hips). The occurrence of total joint replacements did not differ between the FIN-RACo and the SINGLE treatment groups: 6% (95% CI: 2 to 16) vs. 8% (95% CI: 3 to 18) (p = 0.73) during the follow

up. Moreover, two total joint replacements had been performed due to primary osteoarthrosis of the knee and one due to hip fracture.

Table 16. Radiographic damage in different large joints in the two original treatment groups at the 11-year visit (**II**)

	Original randomization group			
	FIN-RACo N = 52		SINGLE N = 54	
Radiographed joint	Unilateral damage	Bilateral damage	Unilateral damage	Bilateral damage
Shoulder	0 (0 %)	2 (4 %)	4 (7 %)	7 (13 %)
Elbow	1 (2 %)	0 (0 %)	1 (2 %)	1 (2 %)
Hip	3 (6 %)	2 (4 %)	4 (7 %)	1 (2 %)
Knee	3 (6 %)	1 (2 %)	2 (4 %)	0 (0 %)

9.4 Other results

9.4.1 The effect of treatment strategies between 2-11 years to consequent outcomes

At 11 years, there was a trend for a more frequent use of oral prednisolone in the SINGLE group compared to the FIN-RACo group (p = 0.076) (Table 13). However, it was not related to the good clinical outcomes; in the SINGLE group 15 % of the patients in remission and 54 % of the patients not in remission were using prednisolone; in the FIN-RACo the respective percentages were group 28 % and 35 %.

The RA patients in the original FIN-RACo group had used a combination-DMARD strategy between 2 and 11 years more frequently than the patients in the original SINGLE group. This, however, had no impact on the frequency of those meeting the modified MDA criteria at 11 years. Those patients of the original FIN-

RACo group who met the modified MDA criteria at 11 years and those who did not, had, after 2 years, received the combination-DMARD strategy for a median of 54 months (95% CI: 46 to 62) and 108 months (95% CI: 101 to 115), respectively ($p < 0.001$). For patients in the original SINGLE group, the median times were 51 months (95% CI: 11 to 91) and 61 months (95% CI: 26 to 96) ($p = 0.71$), respectively.

The same phenomenon could be seen regarding the radiographic results. In both groups, the patients in the tertile of the lowest radiological progression in hands and feet from years 2 to 11 (change in Larsen score 0-1) had received significantly shorter periods of combination-DMARD treatments between years 2 to 11 than the patients with intermediate (change in Larsen score 2-17) or high (change in Larsen score ≥18) progression rates ($p = 0.001$ for linearity in both treatment groups) (Figure 10). A similar trend was found for biological treatments in the entire study population; 14 patients (11 %) had received TNF-inhibitors, of these 1 had low, 5 intermediate and 8 high radiographic progression between years 2 to 11.

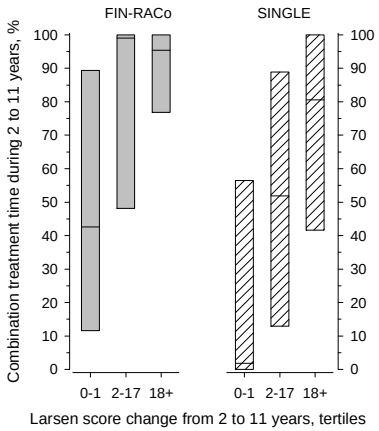

Figure 10. Percentage of treatment time using combination DMARD strategy between year 2 and year 11 in patients of the original randomization groups divided into tertiles according to change in Larsen score of hands and feet from year 2 to year 11. Values are median and interquartile range. (**II**)

9.4.2 Serious adverse events

The number of serious adverse events between years 5 to 11 did not differ between the patients in the original FIN-RACo group and those in the original SINGLE group, neither did the number of all malignancies during the 11 years (Table 17).

Table 17. Serious adverse events between 5-11 years in the two original randomization groups

Adverse event	Original randomization group		P-value
	FIN-RACo (n=68)	SINGLE (n=70)	
Infections	2	4	0.68
Chronic leg ulcer	1	0	
Pneumonia	0	2	
Pyelonephritis	1	1	
Septic arthritis	0	1	
Cardiovascular	5	4	0.74
Acute myocardial infarct / unstable AP	1	2	
Heart insufficiency	2	1	
Cerebral stroke	2	1	
Malignancies	6	4	0.52
Acute myeloid leukemia	0	1†	
Breast cancer	1	0	
Colon cancer	0	2†	
Lung cancer	1†	0	
Lymphoma	1	0	
Multiple myeloma	1	0	
Pancreas cancer	1	0	
Skin basalioma	1	0	
Ventricular cancer	0	1	
Other (hospitalization)	3	2	0.69
ALT elevation	0	1	
Recent diabetes mellitus	1	0	
Pleuritis and pericarditis	1	0	
Urticaria and lung reaction	0	1	
Ventricular ulcer	1	0	

† = death due to SAE; AP = angina pectoris; ALT = Alanine aminotransferase

9.4.3 Comorbidities

The occurrence of comorbidities, such as hypertension, osteoporosis, cardiovascular diseases, or diabetes mellitus did not differ between the groups up to the follow-up of 11 years (Table 18, Figure 11).

Table 18. Comorbidities recorded at the 11-year visit in both original randomization groups

Comorbidities at the 11-year visit, n (%)	Randomization group for the first 2 years	
	FIN-RACo (n = 68)	SINGLE (n = 70)
Hypertension	23 (34)	26 (37)
Osteoporosis	14 (21)	12 (17)
Cardiovascular diseases	10 (15)	9 (13)
Ischemic heart disease	6 (9)	6 (9)
Cerebral stroke	3 (4)	1 (1)
Peripheral vascular disease	0 (0)	1 (1)
Cardiomyopathy	1 (1)	1 (1)
Gastrointestinal events	8 (12)	8 (11)
Diabetes mellitus	6 (9)	6 (9)
Pulmonary diseases	5 (7)	3 (4)
Neurological diseases	0 (0)	2 (3)
Psychiatric disorders	4 (6)	3 (4)

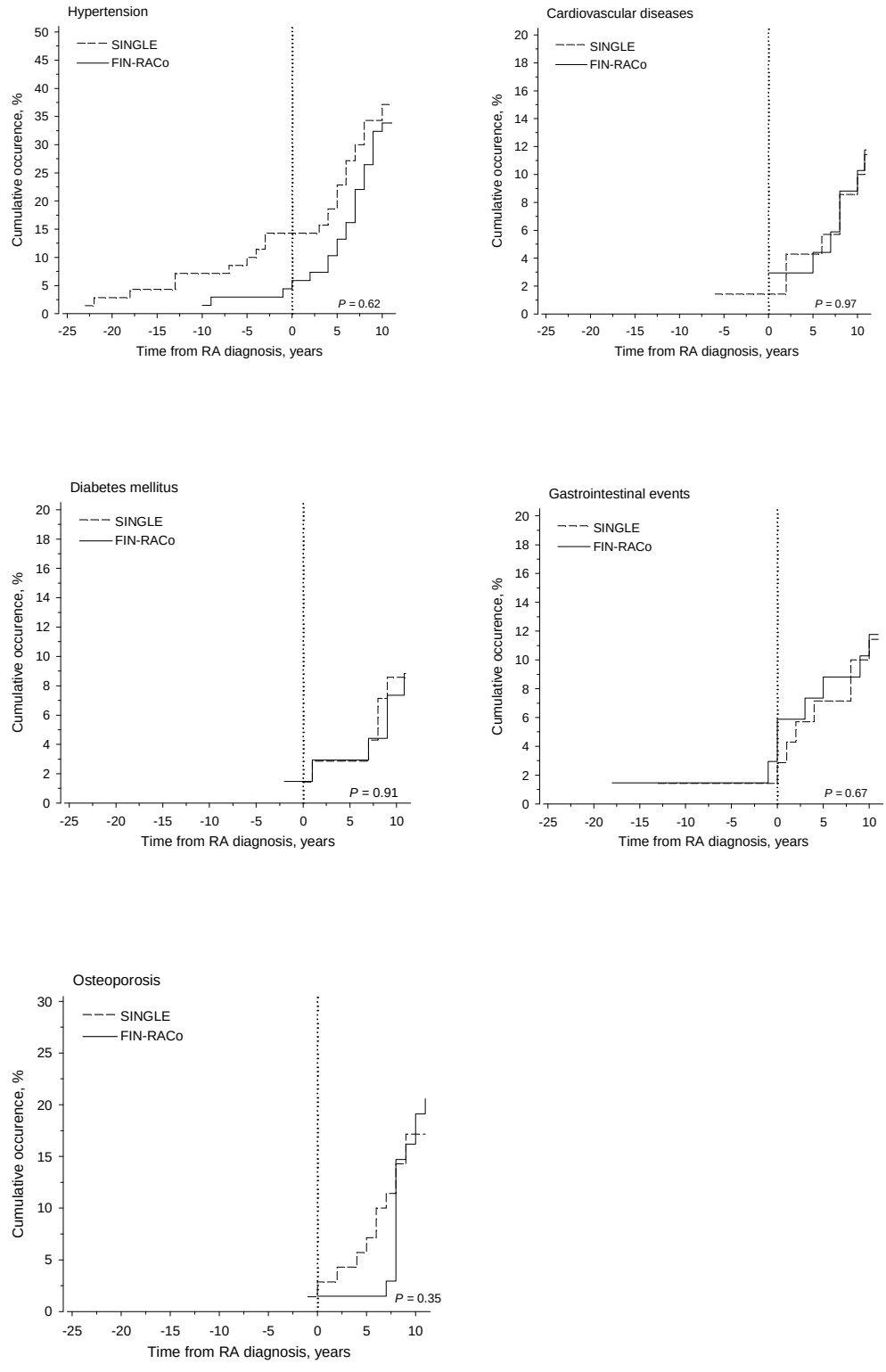

Figure 11. Cumulative incidence of different comorbidities in the 2 original treatment groups. P-values are age and sex adjusted.

9.4.4 Mortality

During the whole 11-year follow-up period, a total of 15 patients had died: 6 in the original FIN-RACo group (6.2% [95% CI: 2.8 to 13.3]), and 9 in the original SINGLE group (9.2% [95% CI: 4.9 to 16.9]). The age- and sex-adjusted hazard ratio was 1.54 (95% CI: 0.54 to 4.39) (p = 0.42) between groups. The age- and sex-standardized mortality ratio in the entire study group was 1.13 (95% CI: 0.64 to 1.87). The reasons for death patients in the original FIN-RACo group were: 2 acute myocardial infarctions, 1 acute arrhythmia (sudden death), 1 dissection of the ascending aorta, 1 pneumonia and exacerbation of chronic bronchitis and emphysema, and 1 malignancy of the lungs, and in the original SINGLE group: 1 acute myocardial infarction, 1 rupture of an abdominal aortic aneurysm, 1 subarachnoid and intracerebral hemorrhage, 2 malignancies of the colon, 1 acute myeloid leukemia, and 3 accidental deaths.

10. Results of the Finnish cohort of early rheumatoid arthritis

10.1 General results

Information of a total of 14 878 patients was assessed. Of these, 9314 (62.6%) had received their reimbursement decision on grounds of RF positive RA and the rest for RF negative disease. The mean (SD) age in the entire patient cohort was 56 (15) years and 10 117 (68.0%) patients were female. From this cohort, the annual incidence of RA in Finland was 44.5/100 000 (95 % CI: 43.8 to 45.2).

10.2 The use of DMARDs in early rheumatoid arthritis in Finland (III)

Throughout all time periods (2000-01, 2002-03, 2004-05 and 2006-07), methotrexate, sulfasalazine and hydroxychloroquine were the three most prescribed DMARDs during the first year of RA; all the other DMARDs had been prescribed

to a substantially smaller percentage of patients (Table 19). Sulfasalazine had been the most often used DMARD in 2000-01, but after that its use had decreased and that of hydroxychloroquine and especially of methotrexate had increased. A total of 69% of new patients with RA received methotrexate during the first year of drug treatment in 2006-07.

Table 19. DMARDs purchased by the Finnish RA patients during the first year after diagnosis (**III**)

Medication during the first 12 months	Years				P for linearity
	2000-01 N=3739 N (%)	2002-03 N=3880 N (%)	2004-05 N=3631 N (%)	2006-07 N=3628 N (%)	
Methotrexate	1639 (43.8)	2079 (53.9)	2330 (64.2)	2505 (69.0)	<0.001
Sulfasalazine	2355 (63.0)	2355 (60.7)	2127 (58.6)	1975 (54.4)	<0.001
Hydroxychloroquine	1879 (50.2)	2045 (52.7)	2056 (56.6)	2169 (59.8)	<0.001
Sodium aurothiomalate	333 (8.9)	204 (5.3)	139 (3.8)	86 (2.4)	<0.001
Auranofin	200 (5.3)	150 (3.9)	76 (2.1)	49 (1.3)	<0.001
Leflunomide	65 (1.7)	140 (3.6)	184 (5.1)	179 (4.9)	<0.001
Azathioprine	51 (1.4)	53 (1.4)	49 (1.3)	40 (1.1)	0.34
Cyclosporine	52 (1.4)	51 (1.3)	43 (1.2)	28 (0.8)	0.012
Podophyllotoxin	19 (0.5)	17 (0.4)	19 (0.5)	28 (0.8)	0.11
Penicillamine	2 (0.1)	3 (0.1)	0 (0)	0 (0)	0.12
Cyclophosphamide	1 (0.0)	7 (0.2)	4 (0.1)	3 (0.1)	0.73
Adalimumab/Etanercept	0 (0)	13 (0.3)	58 (1.6)	38 (1.0)	<0.001

The use of methotrexate, sulfasalazine and hydroxychloroquine alone or in combinations up until 31 days after the index day, i.e., obviously as the very first DMARD or DMARDs (Table 20) was studied. As this very early treatment, the use of methotrexate alone or in combinations increased from 23.5% of the patients in 2000-01 to 56.0% in 2006-07 ($p < 0.001$) (Figure 12). Also the use of glucocorticoids as a very early treatment of RA increased during the follow-up.

Table 20. Treatment with methotrexate (MTX), sulfasalazine (SASP), hydroxychloroquine (HCQ) and glucocorticoids GCs during the first month after diagnosis in Finnish RA patients (**III**)

Medication	Years				P for linearity
	2000-01 N=3739 N (%)	2002-03 N=3880 N (%)	2004-05 N=3631 N (%)	2006-07 N=3628 N (%)	
Single treatment					
MTX	352 (9.4)	392 (10.1)	464 (12.8)	708 (19.5)	<0.001
SASP	1113 (29.8)	1083 (27.9)	789 (21.7)	641 (17.7)	<0.001
HCQ	415 (11.1)	368 (9.5)	296 (8.2)	227 (6.3)	<0.001
Combination treatment					
MTX and HCQ	148 (4.0)	242 (6.2)	312 (8.6)	502 (13.8)	<0.001
MTX and SASP	155 (4.1)	137 (3.5)	187 (5.2)	248 (6.8)	<0.001
SASP and HCQ	229 (6.1)	259 (6.7)	225 (6.2)	249 (6.9)	0.34
MTX, SASP and HCQ	226 (6.0)	324 (8.4)	481 (13.2)	576 (15.9)	<0.001
Glucocorticoids	1379 (36.9)	1591 (41.0)	1637 (45.1)	N.A.	<0.001

N.A. = not available

During the first 3 months the treatments were generally further intensified (Table 21). Only 6.3 % of all patients had not purchased DMARDs during the first 3 months and this non-compliance decreased significantly from 2000-01 to 2006-07. During the study period the use of early single DMARD strategy decreased and the use of early combination DMARD strategy increased (Table 21).

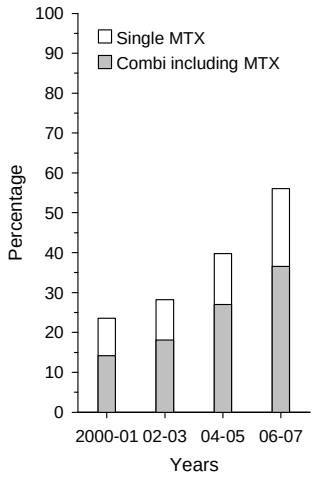

Figure 12. The use of methotrexate alone or in combinations during the first month after the RA diagnosis in different year cohorts.

Table 21. Treatment strategies used during the first 3 months after diagnosis in Finnish RA patients (**III**)

Medication	Years				P for linearity
	2000-01 N=3739 N (%)	2002-03 N=3880 N (%)	2004-05 N=3631 N (%)	2006-07 N=3628 N (%)	
No DMARDs	240 (6.4)	273 (7.0)	245 (6.7)	179 (4.9)	0.0072
Single therapy	2097 (56.1)	2034 (52.4)	1606 (44.2)	1427 (39.3)	<0.001
Combination therapy*	1402 (37.5)	1572 (40.5)	1765(48.6)	2006 (55.3)	<0.001
Adalimumab/Etanercept only TNF-inhibitor	0 (0.0)	0 (0.0)	3 (0.1)	4 (0.1)	ND
and one DMARD	0 (0.0)	1 (0.0)	5 (0.1)	4 (0.1)	ND
and DMARD combination	0 (0.0)	0 (0.0)	7 (0.2)	8 (0.2)	ND

*Two or more DMARDs

Combination DMARD therapy was prescribed more often to seropositive and to younger patients than single DMARD treatment, whereas both genders were treated equally (Table 22).

Table 22. Demographic factors of Finnish patients using different treatment strategies during the first 3 months after RA diagnosis (III)

Variables	No DMARDs N=944	Single therapy N=7174	Combination therapy N=6760	P value
Female, n (%)	629 (66.6)	4867 (67.8)	4623 (68.4)	0.49
Age, mean (SD)	54 (15)	58 (16)	55 (14)	<0.001
Rheumatoid factor present, n (%)	556 (58.9)	4207 (58.6)	4556 (67.4)	<0.001

The use of the FIN-RACo combination (methotrexate, sulfasalazine and hydroxychloroquine) as initial treatment increased throughout the study period

(Table 20). During 2006-07 it was prescribed to 20.3 % of the patients with recent-onset RA within the first 3 months (Figure 13).

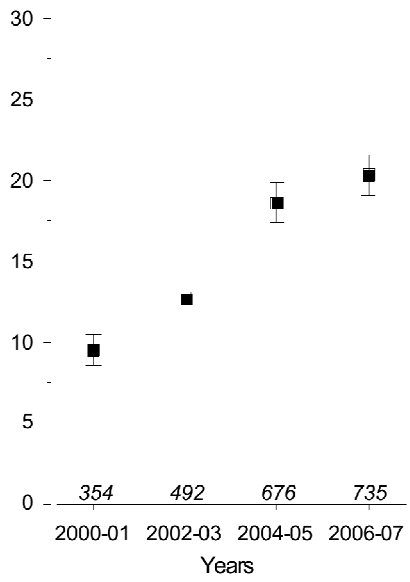

Figure 13. The proportion of Finish RA patients using the FIN-RACo combination during the first three months after the diagnosis (**III**)

The use of adalimumab and etanercept during the first 3 months or even during the first year of RA therapy remained extremely rare throughout the study period (Table 19, Table 21). Reflecting the channelling bias, during the follow-up more of the patients who had received a combination of DMARDs during the first 3 months started a treatment with adalimumab or etanercept [6.7% (95% CI: 5.8 to 7.7%)] than of the patients who had initiated the treatment with a single DMARD [3.4% (95% CI: 2.8 to 4.1%)] or no DMARDs [5.7% (95% CI: 3.8 to 8.4%)] ($p < 0.001$, adjusted for age, sex, RF-positivity) (Figure 14).

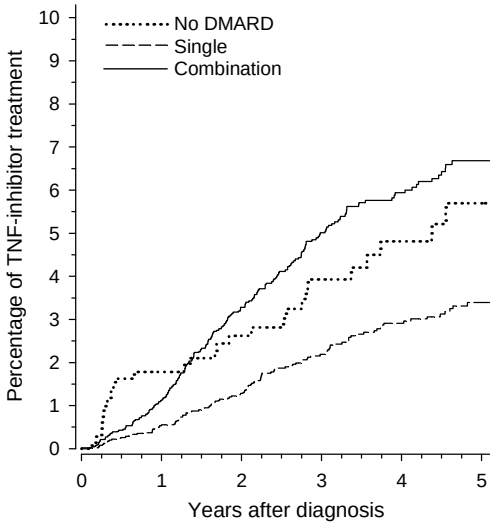

Figure 14. The cumulative introduction of adalimumab or etanercept with regard to the initial antirheumatic treatment during the first 3 months.

10.3 The maintenance of working ability in early rheumatoid arthritis in Finland (IV)

A total of 7831 (71% female, 61% RF-positive) working-aged (18-64 years), and at index date full-time available to work force RA patients were identified. An additional cohort of 137 patients, already part-time retired at the index date, was included in the analysis of mean annual WD days. Table 22 presents the demographic data. During the follow-up, the use of combination-DMARDs during the first 3 months increased, while that of single-DMARD treatment decreased. The use of MTX, either alone or in combinations, increased. The admission of adalimumab or etanercept for patients remained rare (Table 22).

Table 22. Demographic data and initial treatment strategies of the 7831 patients with a recent diagnosis of RA, available to labour force at baseline (**IV**)

Variable	Year cohort			
	2000-01 (N = 1998) N (%)	2002-2003 (N = 2043) N (%)	2004-05 (N = 1871) N (%)	2006-07 (N = 1919) N (%)
Female (%)	1422 (71)	1462 (72)	1291 (69)	1377 (72)
Age on index day, mean (SD)	45 (11)	46 (11)	47 (10)	46 (11)
Rheumatoid factor present (%)	1135 (57)	1235 (60)	1161 (62)	1242 (65)
Initial treatment (≤ 3 months)				
No DMARDs	149 (7)	171 (8)	145 (8)	113 (6)
Single DMARD	1072 (53)	1004 (49)	750 (40)	708 (36)
MTX	166 (8)	196 (10)	243 (13)	295 (15)
Combination DMARDs	781 (39)	877 (43)	989 (53)	1105 (58)
Including MTX	502 (25)	651 (32)	801 (43)	925 (48)
Etanercept or adalimumab initiated at any time while available to labour force	79 (4)	84 (4)	85 (5)	29 (2)

DMARD = disease modifying anti-rheumatic drug, MTX = methotrexate, SD = standard deviation

During the first year after RA diagnosis, the mean number of annual WD days per patient years was similar in all year cohorts, 45-50 days per year. During the second year it decreased, and again increased steadily thereafter (Figure 15). During the second year the mean number of annual WD days per patient years decreased along the year cohorts ($p = 0.002$ for linearity, adjusted for age, sex and RF).

When analysing the data of all cohorts during the first two years together, the number of the mean annual WD days per patient years was 53 in men, and 37 in women [mean ratio between men and women 1.42 (95 % CI: 1.28 to 1.54)], while 45.6 (95% CI: 43.6 to 47.6) of the men and 48.2 (95% CI: 46.9 to 49.5) of the women had no registered WD days during the first 2 years after the RA diagnosis.

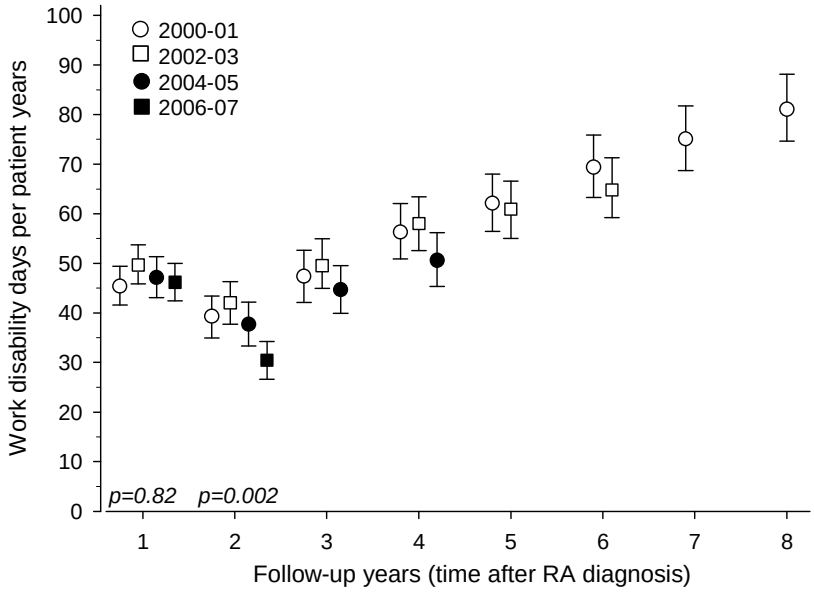

Figure 15. Mean annual WD days per patient years in the early RA cohorts. The values are presented as means with 95% confidence intervals (**IV**)

The median (IQR) follow-up time was 4.0 (2.2 , 6.3) years. By 8 years 14.5% (95% CI: 13.5 to 15.5) patients of the total patient population had prematurely retired due to RA. In the female population the cumulative incidence of RA dependent continuous WD was 12.6 % (95 % CI: 11.5 to13.7) and in males 19.2 % (95 % CI: 17.1 to 21.4) [age and RF adjusted HR = 0.68 (0.59 to 0.78), p <0.001] (Figure 16).

During the first 2 years after the index day, the incidence of RA related continuous WD was 8.9 % (95 % CI: 7.7 to 10.3), 9.4 % (95 % CI: 8.2 to 10.8), 7.2 % (95 % CI: 6.2 to 8.5), and 4.8 % (95 % CI: 3.9 to 5.9) in the year cohorts 2000-01, 2002-03, 2004-05, and 2006-07, respectively (age, sex, and RF adjusted p < 0.001 for linearity). Figure 17 presents the Kaplan-Meier curves for permanent WD in different year cohorts during the 8-year follow-up.

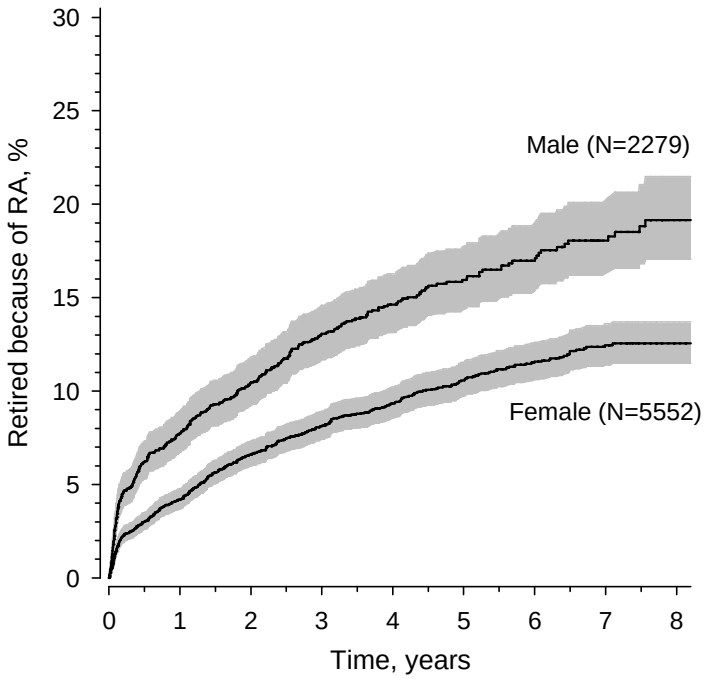

Figure 16. Kaplan-Meier curves and confidence intervals of the incidence of RA related work disability in the male and the female patients after the diagnosis of RA (**IV**)

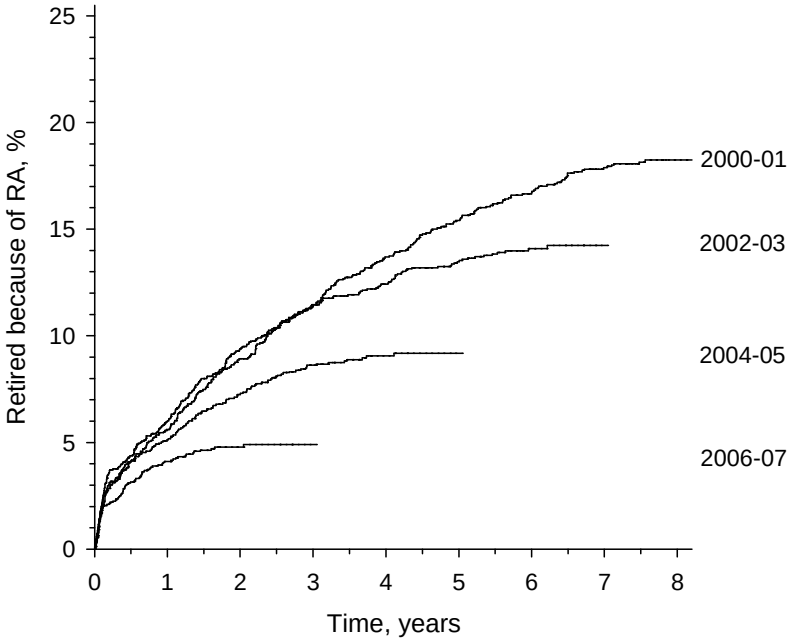

Figure 17. Kaplan-Meier curves of the proportions of patients prematurely retired due to RA in different recent RA patient cohorts. In a Cox regression analysis each cohort had a lower risk for permanent working disability than the preceding one ($p < 0.001$ for linearity) (**IV**)

In a Cox multivariate analysis for the 8-year follow up, the year cohort, higher age, and male gender were related to premature retirements (Table 24). In the same model, when single non-MTX DMARDS as initial treatment was used as reference, undoubtedly due to the confounding effect of indication, all the other active initial treatment strategies (but not no-DMARDs) significantly increased the risk of premature retirements. However, despite this channelling bias, etanercept and adalimumab appeared to protect the patients from premature retirements (Table 24). During the follow-up, they were prescribed to 277 patients [70 % female, mean (SD) age on index day 41 (12)] while still available to labour force and were started on average 2.6 (SD 1.8) years after the index day.

Table 24. Cox multivariate regression analysis on factors predicting premature retirement in the Finnish early RA cohort (**IV**)

	HR (95% CI)	*p*-value
Age	1.08 (1.07 to 1.09)	<0.001
Male	1.50 (1.30 to 1.72)	<0.001
RF present	1.10 (0.96 to 1.27)	0.18
Year cohort		<0.001*
2000-01	1 (reference)	
2002-03	0.79 (0.68 to 0.93)	
2004-05	0.52 (0.43 to 0.63)	
2006-07	0.36 (0.28 to 0.45)	
Medication (first 3 months)		<0.001
Single other	1 (reference)	
Single MTX	1.35 (1.07 to 1.71)	
Combi other	1.28 (1.02 to 1.62)	
Combi including MTX	1.53 (1.29 to 1.81)	
None	1.18 (0.89 to 1.55)	
Etanercept or adalimumab initiated at any time while available to labour force	0.61 (0.39 to 0.96)	0.034

* p for linearity

The incidence of premature work disability pension for any reason in the entire working aged Finnish population remained stable; it was 0.7 % in 2000 and 0.8% in 2008. When comparing our early RA population to the entire working aged Finnish population, the age and sex stratified standardized incidence ratio (SIR) for a premature disability pension was 3.16 (95 % CI: 2.97 to 3.35) and it declined along the year cohorts; it was 3.69 (95 % CI: 3.35 to 4.04), 3.34 (95 % CI: 2.99 to 3.71), 2.77 (95 % CI: 2.40 to 3.19), and 2.80 (95 % CI: 2.29 to 3.39) for the year cohorts 2000-01, 2002-03, 2004-05, and 2006-07, respectively (p for linearity < 0.001) (Figure 18).

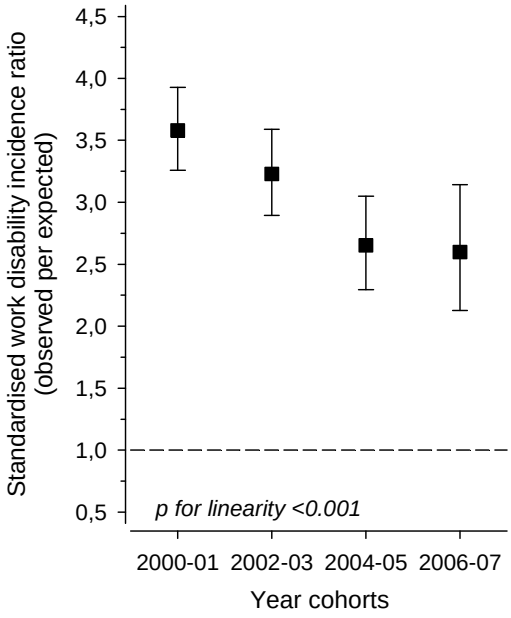

Figure 18. The standardised incidence ratio (SIR) for a premature disability pension in the Finnish early RA patients compared to the general Finnish population. The values are presented as means with 95% confidence intervals (**IV**)

DISCUSSION

11. General discussion

With the perfect, curing, therapy of RA still lacking, the current treatment of RA should remove the inflammatory symptoms rapidly and safely, prevent permanent damage, and be financially available to all patients. Furthermore, as RA is a chronic, lifelong disease, all of these prerequisites should be met even in long-term. The studies on long-term (>10 years) clinical outcomes in early RA are, however, few and most of them have neither a definite nor an active treatment protocol, thus representing the course of conservatively treated RA (Jacoby et al. 1973, Corbett et al. 1993, Drossaers-Bakker et al. 1999, Jäntti et al. 2002, Lindqvist et al. 2002). Nonetheless, to justify the use of therapies potentially bothersome to the patient and burdening to the health care resources, long-term results of patients treated with the contemporary, active treatment protocol are of great importance.

12. The FIN-RACo Trial 11-year follow-up

12.1 Patient selection and methods

When estimating the effects of different treatments, it is essential that the patients represent the true disease and that the treatment effect may be estimated. The patients participating in the FIN-RACo trial had a definite diagnosis of RA as they were fulfilling the ACR criteria, which have even been criticised for missing the early phases of the disease (Aletaha et al. 2010). Also, at baseline the patients had an active RA with a minimum of 3 swollen joints, the mean SJC being 13 in both groups, indicating a potentially progressive disease (Welsing et al. 2004). Thus, a spontaneous recovery of the symptoms is implausible (Symmons and Silman 2006) and the effect of different treatment strategies may reliably be estimated.

The baseline clinical and demographic variables were similar in both groups. However, for unknown reason the dropout patients in the FIN-RACo group had a higher Larsen score at baseline than the patients completing the study, in whom there was a trend towards a lower Larsen score at baseline compared to the SINGLE group completers. To neutralize the possible bias caused by this trend, the statistical analyses on radiographic outcomes were adjusted with the baseline Larsen score.

Throughout the follow-up the functional ability was assessed with a valid method, the HAQ score (Wolfe 2001). For defining remission the ACR criteria (Pinals et al. 1981) were used, with the exclusion of the fatigue criterion and with the requirement of fulfilment of all the remaining criteria. Thus, a patient in remission had practically no signs of the disease, a very strict definition (Mäkinen et al. 2005a), seldom fulfilled even by normal elderly people (Sokka et al. 2007a). This must be kept in mind when comparing our results to those of others with less strict definitions of remission, such as the widely used DAS28 score below 2.6, which may still allow significant disease activity (Mäkinen et al. 2005b).

Larsen score was used for the evaluation of the radiographic damage. On one hand, this method has been found to be less sensitive to change than the currently widely used Sharp/van der Heijde method (Bruynesteyn et al. 2002, Guillemin et al. 2005), but, on the other hand, the Larsen method tends to be more specific than the Sharp/van der Heijde method (Bruynesteyn et al. 2002). With as long a follow-up as 11 years, specificity was preferred over sensitivity; it is more important to distinguish clinically relevant from unspecific changes than to find subtle joint space narrowing. Also, the intraobserver reliability in Larsen score is somewhat better than that of the Sharp/van der Heijde method (Sharp et al. 2004, Guillemin et al. 2005), and having had the same experienced radiologist scoring the radiographs

with the Larsen method throughout the follow-up, the use of this method was found logical. Further, to our knowledge there are no other valid methods for evaluating the radiographic progression in large joints besides the Larsen method.

The extension of a trial originally planned to continue for 2 years is by no means without problems (Landewe 2010). Different confounders may have affected how the patients are treated, as well as which patients continue the follow-up and which drop out of it. Thus, it is important to recognize these possible flaws, and when possible, try to overcome them by different statistical methods. Still, more important than to concentrate on the possible differences between the groups, we should emphasize the impact of retarding disease progression in all RA patients. After all, the FIN-RACo trial, launched 15 years before the rest of the world's rheumatologists reached a consensus on treating RA to target (Smolen et al. 2010b), gives invaluable and accurate information on the results reached by such protocol in real life and in long-term.

12.2 Clinical and radiographic outcomes

In this study, after the initiation of treatment, most of the patients in both study groups had low HAQ scores throughout the follow-up reflecting well-preserved functional ability. At 11 years approximately half of the patients had a HAQ score of zero, having thus no disability, which is an excellent result, especially when keeping in mind that HAQ scores increase with age even in a normal population (Sokka et al. 2006). In previous long-term follow-up studies of early, conservatively treated RA the HAQ scores have shown an increasing course (Drossaers-Bakker et al. 1999, Welsing et al. 2001, Lindqvist et al. 2002). However, contemporary studies with shorter follow-up and active treatments with either a single DMARD (Scott and Strand 2002), combinations of conventional DMARDs (Boers et al. 1997,

Landewe et al. 2002), or biological agents (St Clair et al. 2004, Breedveld et al. 2006) have shown functional improvement along with the induction of treatment. Furthermore, cross-sectional studies comparing recent RA cohorts to earlier ones have found a tendency toward better-preserved functional ability during the present time (Sokka et al. 2000, Krishnan and Fries 2003) and a predictive role of strict remission on protection of functional ability (Scire et al. 2011). Our results thus confirm the benefit from continuous active treatment strategy on preserving functional ability even in long-term.

At 11 years, most of the patients in both study groups had low parameters of disease activity and approximately half of them achieved remission according to the DAS28 criteria (Prevoo et al. 1995). Even though not otherwise comparable, similar proportions of early RA patients treated with a combination of a biologic and MTX have reached the DAS28 remission in 1-2 years of follow-up (Breedveld et al. 2006, Emery et al. 2008).

However, the main outcome measure of this study was the strict ACR remission, which was reached by a substantial proportion of the patients in both study groups at some point during the follow-up. The sustainability of remission was, nevertheless, more frequent in the FIN-RACo group, whereas never having achieved remission was more common in the SINGLE group. Still, even somewhat surprisingly, the proportion of patients in strict remission at 11 years was as high as 37 % in the FIN-RACo group, while it was 19 % in the SINGLE group; quite similar a figure than in an earlier Swedish study where the proportion of patients in remission was 18 % after 10 years of RA (Lindqvist et al. 2002). Yet, variations between remission and no remission were relatively common in both treatment groups, probably because a considerable number of patients were near the limit of remission most of the time

and, coincidently on either side of the remission limit at the study visits, as illustrated by the disease activity parameters. This is logical, since the therapy in both groups was aimed at remission and the treatment armament was open. Nonetheless, it appears that early and active treatment is especially worthwhile, as the remission reached at 6 months predicted the remission in the FIN-RACo group even at 11 years in this study. One more indicator of successful treatment, the presence of modified MDA (Wells et al. 2005), was at 11 years achieved by more patients in the FIN-RACo group than in the SINGLE group. Also there, the presence of modified MDA at 2 years predicted this outcome at the end of the follow-up, especially in the FIN-RACo group.

For radiographic damage, the main finding of the present study was the low radiological progression in both groups compared to earlier cohorts. In a Finnish cohort from the Heinola Rheumatism Hospital, 103 patients with early RA starting from the 1970s were followed up for 20 years (Kaarela and Kautiainen 1997) and found to have the steepest radiographic progression during the first 8 years, even though it continued throughout the follow-up. In that cohort, the mean ± SD Larsen score at 3 years was 27 ± 21, thus comparable to that of our patients at 11 years. In another Finnish cohort, treated with the saw-tooth method and starting the treatment in 1980s the mean Larsen score was approximately 36 after 10 years and 44 (95% CI: 36 to52) after 15 years of RA (Tiippana-Kinnunen et al. 2011). In a Swedish cohort from the 1980s, 181 patients with conservatively treated early RA had at 10 years a median Larsen score of 54 (IQR 28–80) (Lindqvist et al. 2003), thus double the Larsen score of our patients at 11 years. Consequently, the findings of our study support the analyses of Finckh et al. (2006a) who found that during the past decades the radiographic prognosis of RA has improved in parallel with more active

treatments. There are other contemporary long-term follow-up studies on radiographic progression in patients with early RA treated with conventional DMARDs, but as they have utilized the Sharp van der Heijde method, direct comparisons with our results are problematic (Drossaers-Bakker et al. 2002, Syversen et al. 2008, Hoff et al. 2009, Hafstrom et al. 2011).

Still, even though the progression of joint damage was moderate in both groups, the FIN-RACo patients had significantly lower increase in the median Larsen score from baseline to 11 years than the SINGLE patients; and in addition to the presence of rheumatoid factor, only the initial SINGLE treatment predicted the radiographic progression at 11 years in an ordered logistic regression analysis. The main difference between the groups had developed during the first 2 years; after that both groups progressed at a similar rate; additionally, remission achieved at 1 year predicted a lower rate of radiographic progression in either group. The difference in radiographic damage may also explain the differences in the remission rates; radiographic damage causes tender joints and thus excludes the fulfilment of the remission criteria.

These findings emphasize the effect of rapid and effective intervention; damage once arisen cannot be undone. The BeSt trial has produced comparable conclusions; even though the clinical outcomes at 5 years were similar between the 4 treatment arms, the radiographic damage was smaller in the 2 combination groups (Klarenbeek et al. 2011), in which the induction of low disease activity had succeeded more rapidly than in the monotherapy arms (Goekoop-Ruiterman et al. 2005). The 11-year analysis of the COBRA trial concentrated in safety issues, but found also some sustained benefit on radiographs in the COBRA treatment arm (van Tuyl et al. 2010b). Nevertheless, the slow progression rate noted in the

contemporary studies raises the question of whether the law of diminishing marginal utility could be applied even to medicine; is it cost-effective or ethical to recommend exceedingly expensive and at least theoretically hazardous biological treatments to a large proportion of patients to achieve slightly lower progression rates than noted with these protocols (Yazici et al. 2009)? Undeniably, however, there is a minority of patients with refractory disease requiring treatment with biologics.

Damage to large joints correlates with decreased functional ability (Drossaers-Bakker et al. 2000). In the present study 87 % of the FIN-RACo and 72 % of the SINGLE patients had no radiographic damage in large joints. This is substantially less than in the few earlier long-term studies on large joint damage in early RA. In 1997, Kuper et al. found radiographic damage in large joints in 20 % of the patients after 1 year of RA, and in 50 % after 6 years of RA (Kuper et al. 1997). In a Dutch study only 30% of the patients had no radiographic abnormalities in large joints, 54 % of patients had at least one eroded large joint, and 14 % had at least one total joint replacement after 12 years of RA (Drossaers-Bakker et al. 2000). Recently, Tiippana-Kinnunen and colleagues published data on 86 Finnish early RA patients treated according to the saw-tooth method; 45 % of these patients had damage in large joints after 15 years of RA (Tiippana-Kinnunen et al. 2011). In the present study the infrequent destruction of large joints was also reflected in the small number of total joint replacements in both of our treatment groups compared to earlier cohorts (Wolfe and Zwillich 1998).

12.3 Safety

The results of the FIN-RACo Trial indicate that even in long-term therapy with combinations of conventional DMARDs is safe. No unexpected adverse effects

occurred in either group after 2 (Möttönen et al. 1999), 5 (Korpela et al. 2004), or now after 11 years of treatment. What is more, the observed mortality rate was equal to that in the general population, thus not increased, which is consistent with some previous studies (Sokka et al. 1999b, Kroot et al. 2000, van Nies et al. 2010). The incidence or prevalence of comorbidities did not differ either between the groups, not even that of osteoporosis, hypertension or type 2 diabetes, thus the possible adverse events of long-term GC administration. The incidence of hypertension had started already before the diagnosis of RA; the other comorbidities emerged after the RA diagnosis. The prevalence of osteoporosis, hypertension, or that of type 2 diabetes is similar to that reported in other cohorts (Briggs et al. 2009).

12.4 The significance of the treatment strategy

The differences in treatment strategies between the groups lay in the use of either a combination of 3 DMARDs or a single DMARD during the first 2 years. Otherwise both groups were treated equally actively with the target in remission, with the medications adjusted and intra-articular as well as systemic GCs administered accordingly. Prednisolone was part of the initial treatment protocol in the FIN-RACo group, and discretionary in the SINGLE group. However, majority of the SINGLE group patients used prednisolone from the very beginning, and by the end of 2 years initial follow-up, more patients in the SINGLE group were using systemic GCs and had a higher cumulative dose of intra-articular GCs than in the FIN-RACo group (Möttönen et al. 1999).

After 2 years the therapies could be modified without restrictions. At 11 years, similar treatments were used in both groups. However, partly due to the protocol allowing the tapering of only 1 DMARD per year in a FIN-RACo group patient with RA in remission, the FIN-RACo group patients used more often combination-

DMARDs than the SINGLE group patients between 2-11 years. Another possible reason for this difference may have been a relative non-compliance in some SINGLE group patients having got used to the treatment with a single-DMARD and having low disease activity, even though not being in remission. Still, it appears that the difference in treatment strategies between 2-11 years had no impact on the clinical or radiographic outcomes at 11 years. In fact, in the FIN-RACo group, the patients achieving the modified MDA criteria at 11 years had received significantly less combination treatments between 2-11 years than the patients not achieving the modified MDA criteria at 11 years. In the SINGLE group, the treatment strategy between 2-11 years did not affect on the frequency of modified MDA at 11 years. Correspondingly, the patients with the least radiological progression after 2 years had used the shortest periods of combination DMARDs after 2 years.

The short-term benefit of combining MTX, SASP, and HCQ was first demonstrated in established RA (O'Dell et al. 1996), but subsequently also as initial treatment in early disease in the FIN-RACo trial (Möttönen et al. 1999), by Calguneri et al. (1999), and later in a real life setting (Proudman et al. 2007). However, in a study by Saunders et al. (2008), stepping up to triple combination was as effective as initiating with it, when an otherwise active treatment strategy with frequent intra-articular GCs was utilized. Still, in that study, the DAS28 remission rates at 12 months were 45 % in the step-up group and 33 % in the initial triple-therapy group, thus somewhat lower compared to the CIMESTRA Trial, which at 2 years had a DAS remission rate of 50 % (Hetland et al. 2008). Further, the 5-year results of the CIMESTRA Trial show a DAS remission rate of 78 %, ACR remission rate of 56 %, while 17 % of the patients had been able to withdraw treatment due to remission (Hetland et al. 2010). Corresponding results were

achieved with the intensified COBRA strategy, having the DAS28 remission rate at 90% at week 40 (van Tuyl et al. 2008), as well as in the Finnish NEO-RACo Trial (Leirisalo-Repo et al. 2008), where 100 early RA patients were treated with intensified FIN-RACo protocol and intraarticular GCs, and randomized to receive either infliximab or placebo infusions for the first 6 months. The results of this trial have thus far only been published in abstract form, but they show that after 2 years 53 % of the FIN-RACo treated patients were in strict ACR remission and had a mean change in Sharp/van der Heijde score from baseline of 1.4. For the patients receiving the FIN-RACo treatment plus infliximab for the first 6 months, the remission rate was 70 % and the change in Sharp/van der Heijde score -0.2. The proportion of patients in DAS28 remission was 82 % in both groups (personal communication, M. Leirisalo-Repo).

The concept of minimising the cumulative inflammation time crystallises the ideal contemporary treatment of RA (Kiely et al. 2009a). This approach includes initiating the treatment as soon as possible (Möttönen et al. 2002, van der Linden et al. 2010, Bosello et al. 2011), treating the disease as effectively as possible, monitoring the response and aiming at the lowest possible disease activity (Knevel et al. 2010). There is a broad consensus on the importance of these principles; however, the real life resources may pose limitations for their execution. Setting the diagnosis early is challenging, while an unequivocal diagnostic test is thus far lacking, and financial facts restrict the frequency of control visits as well as the repertoire of available medications.

Various single DMARDs have been proven effective in clinical trials; still, in an individual patient, the efficacy of a given medicine may not be estimated in advance (Hider et al. 2009), but has to proven suitable by trial and error. And when an either

poorly tolerated or ineffective initial therapy has to be changed to another, valuable time is lost to active inflammation during the therapeutic "window of opportunity" in early RA. Therefore, the point of early, initial combination treatment lies in its sustainability; even if one DMARD has to be discontinued because of side effects, the patient still has another DMARD working, and at best, all the initiated DMARDs are tolerated and having additive efficacy. When using tight treatment strategy and intra-articular GCs, however, the benefit of initial combination treatment is diminished (Hetland et al. 2008, Saunders et al. 2008). Nonetheless, monthly visits to all early RA patients are seldom possible, and unfortunately not all rheumatologists are enthusiastic about time-consuming intra-articular injections, probably due to strict work schedules. The results of the FIN-RACo trial are thus in this respect reassuring, suggesting that possibly by utilising the initial combination treatment, good results may be achieved without an excess need for intraarticular or peroral GCs or treatment adjustments. Therefore, with real-life resources, starting the initial FIN-RACo combination appears to pay off, even in the long run, especially when the side effects are not more frequent or serious than with a single DMARD. Also others (Graudal and Jurgens 2010, Tosh et al. 2011), but not all (Katchamart et al. 2009), have settled on recommending initial combination treatment in early RA.

Nevertheless, the importance of combining small-dose GCs to the other treatment of early RA is indisputable (Kirwan et al. 2007). Our results, as well as those of the COBRA 11-year follow-up (van Tuyl et al. 2010b) prove that the safety profile of such an approach is acceptable. However, for minimising the possible adverse effects, intra-articular administration of GCs may be recommended. Such strategy was very actively utilised in the CIMESTRA trial, which has thus far shown

excellent clinical results during up to 5 years of follow-up (Hetland et al. 2010). In the CAMERA trial the use of GCs was deliberately avoided, which may explain somewhat inferior results; another possible explanation for achieving mediocre results with a supposedly active and steered treatment strategy is allowing too high a disease activity before adjusting the therapy (Verstappen et al. 2007, Bakker et al. 2011). True, significant remission and radiographic non-progression are seldom achieved by aiming at an improvement less than 100 %, or by targeting "low disease activity" measured by DAS28, a method not assessing the feet joints and, at worse, allowing several of the assessed joints to be swollen even in "remission" (Mäkinen et al. 2005b).

Today, the FIN-RACO protocol may be criticised for starting the initial single-DMARD treatment with SASP; possibly different results would have been achieved in the SINGLE group had the first DMARD been MTX. However, in 1993, when the FIN-RACo Trial begun, the clinical use of MTX in RA was far less common than today, and there were no studies showing its superiority compared to other DMARDs. Even a recent review (Donahue et al. 2008) found no evidence of the superiority of MTX in comparison with other DMARDs in clinical efficacy. More importantly, in the FIN-RACo Trial, the SINGLE strategy was not tied to SASP but to a strategy of using 1 DMARD at a time. Consequently, during the first 2 years, 52 % of the SINGLE group patients were switched to MTX, and some of these even further to another DMARD (Möttönen et al. 1999).

13. The Finnish early RA register studies

13.1 Patient selection and methods

The great strength of these studies is that practically all Finnish new RA patients were included, thus the representativeness of the data does not need to be

questioned. The weakness of this register-based study is the lack of clinical and radiographic data. Thus the medications prescribed cannot be related to the disease activity noted; only to the patient's age, gender and the presence of RF. However, WD is one of the most significant outcomes of RA (Verstappen et al. 2004), and for that the current study had highly reliable and representative data. One shortcoming of this official registry-data is that data on short (<10 days) sick leaves were not available, since they are not registered by the SII. Also, for natural reasons, the follow-up time for the latest cohort for the assessment of continuous WD was shorter than for other cohorts. This was, however, controlled by statistical methods.

The incidence of RA was in this study somewhat higher than in an earlier Finnish report (Kaipiainen-Seppänen and Kautiainen 2006). Thus, hardly many RA patients are left out of this analysis, quite the opposite. The contemporary emphasis on early diagnosis of RA (Puolakka et al. 2005b, Finckh et al. 2006b, van Dongen et al. 2007, Finckh 2009) may have caused that our cohort includes patients who do not fulfil the ACR criteria for RA (Arnett et al. 1988), but were, due to typical clinical picture, the presence of ACPA, or due to some other feature, judged to represent very early RA by a rheumatologist, who considered the introduction of DMARD therapy necessary. On the other hand, the incidence of RA may truly be rising (Myasoedova et al. 2010). Either way, as the cohorts do not differ in size, nor in demographic variables, it appears that the criteria for the drug imbursement decisions have remained similar throughout the follow-up, and thus comparing the groups is justified.

The methods of studying and reporting the use of DMARD are varying, making the comparison between studies challenging. However, in this study the following time points for analysing the DMARDs prescribed were found valid: the initial, first

treatment (from one month before to one month after the diagnosis); the probable first modification (within the first 3 months after the diagnosis); and the established treatment (within the first year after the diagnosis). For analysing the incidence of WD, the methods in different studies are also heterogeneous. In the present registry-based study the scale and evolution of this phenomenon could be assessed with great accuracy, even though the reasons behind it could not.

13.2 The use of DMARDs in Finland

In the present study it could be found that in Finland, in accordance with national guidelines (Current Care Guideline 2009) and with international trends (Sokka et al. 2008), all the indicators of treatment policy had changed towards more active ones: single DMARD as the most often used initial strategy was replaced by combination DMARDs, MTX substituted for SASP as the most used DMARD, the use of GCs increased somewhat and the proportion of patients not receiving DMARDs within the first 3 months decreased. This progression is not overly unexpected since Finnish rheumatologists have had a tradition of treating RA aggressively (Albers et al. 2001, Sokka et al. 2007b), already from 1970s (Luukkainen et al. 1977), and increasingly so after the publication of the favorable results of the FIN-RACo study (Möttönen et al. 1999, Möttönen et al. 2002, Korpela et al. 2004, Puolakka et al. 2005a). The participation of all the large Finnish rheumatology centers to the FIN-RACo Trial might also explain the success of the implementation of this strategy to everyday practice compared to, for example, what the COBRA strategy has faced in the Netherlands (van Tuyl et al. 2007).

Others, too, have found, that implementing recommendations or positive study results to everyday practice is not always self-evident (Kvalvik et al. 2001, Schmajuk et al. 2007, Kiely et al. 2009b, Tavares et al. 2011). Therefore, wide

feedback of the success of the current recommendations in real-life would be, in a sense, an assurance of their quality and, more importantly, a prerequisite for future actions.

Studies from the last millennium give, in this respect, merely a historical perspective of the earlier treatment of RA (Berard et al. 2000, Kvalvik et al. 2001, Edwards et al. 2005). Of the more recent studies, the ones interviewing rheumatologists give an idea of the degree of agreement with the recommendations (Jobanputra et al. 2004, Maravic et al. 2004, Fraenkel et al. 2006). However, the clinicians may report more idealistic treatment strategies than the ones they actually use, and further, not all RA patients are treated by specialists, a fact to be taken into account when considering the results of smaller, hospital-based cohorts (Ward 1999, Kvalvik et al. 2001, Aletaha and Smolen 2002, Saraux et al. 2002, Sokka and Pincus 2002, Carli et al. 2006, Yamanaka et al. 2007). Thus, large population based cohorts of RA patients would give a more realistic view of the current DMARD policy. In many of such studies, however, the patient populations may be heterogeneous in terms of disease durations (Edwards et al. 2005, Schmajuk et al. 2007, Ziegler et al. 2010, Neovius et al. 2011a).

The results of earlier, large cohort studies have given rather a nihilistic view on the treatment of RA; in the 1990s' only 13 % (Berard et al. 2000) to 50 % (Edwards et al. 2005) of the patients with established RA were receiving DMARDs. More recent cohorts prove, however, that the situation has improved. In a private US clinic, the 5 practicing rheumatologists prescribed MTX as the first DMARD to 82.3 % of the early RA patients between 1998 and 2001 (Sokka and Pincus 2002). In a Swedish study carried out between 1997 and 2001 in 19 different hospital clinics, the prescriptions of DMARDs, especially of MTX, increased, and the proportion of

patients with early RA not prescribed any DMARDs decreased from 32.2 % to 14.9 % (Carli et al. 2006). The Norfolk Arthritis Register (NOAR) showed that the treatment of early inflammatory polyarthritis has intensified from the 1990s' to this millennium, but even in the last cohort, diagnosed 2000-2004 and followed up for 5 years, 28.1 % of the patients had never received DMARDs (Scire et al. 2011); on the other hand, not all of the patients had RA. In another UK cohort of early RA patients between 2002-2007, 97 % of the patients were initially prescribed a DMARD; 91 % monotherapy (51 % MTX, 41 % SASP), and 9 % combination therapy, and for the 33 % of the patients requiring treatment intensification, 52 % were prescribed sequential monotherapy and 48 % step-up combination therapy (Kiely et al. 2009b). For patients with established RA, in 2000-2006, in a single-institute-based Japanese cohort the use of DMARDs increased from 82.2 % to 89.6 %, and the proportion of MTX users increased from 33.9% to 58.7% (Yamanaka et al. 2007). A very large German study on cross-sectional cohorts of altogether 38 723 patients with established RA between 1997-2007 showed that the proportion of patients receiving no DMARDs remained quite stably at 15 %, the proportion of patients on DMARD monotherapy decreased from 74.3 % to 61.8 %, and on DMARD combinations increased from 7.5 % to 22.3 % (Ziegler et al. 2010). The use of MTX was approximately 56 % throughout the follow-up, and approximately half of the patients were using GCs, but the proportion of patients using GC only increased from 5 to 8 %. Biologics were not available at the beginning of the study, but were used by 16 % of the patients in the latest cohort. In an even larger study, Neovius et al. analyzed the data of 58 102 prevalent Swedish RA patients, and reported that during the preceding 3 years, 76 % of the patients had been treated with DMARDs, GCs or biologics; thus 24 % had not received any antirheumatic

treatment during that time (Neovius et al. 2011a). The penetration of DMARDs or biologics also decreased with age, a finding in accordance with others (Fraenkel et al. 2006), and seen also in our results. To conclude, even during the present era marked national variations in the treatment of RA exist, but worldwide the strategy has unquestionably changed towards a more active one.

Compared to the above-mentioned results of others, the Finnish rheumatologists appear to treat early RA remarkably actively. Especially the use of initial DMARD combinations is markedly higher than in any other reports. Thus, it appears that the FIN-RACo philosophy to treat the patient early, to use initial DMARD-combinations and low dose GC, and to target true remission has gained ground throughout Finland. Supposedly the good clinical results achieved by this strategy have also caused many Finnish rheumatologists (Current Care Guideline 2009) to shun the straightforward EULAR recommendation of inducing a biologic to a patient failing single MTX (Smolen et al. 2010a), even though the need of biological intervention is recognised in a patient failing treatment with a combination of DMARDs including MTX (Current Care Guideline 2009).

13.3 Working ability

In this study it could be found that the frequency of permanent disability pensions due to early RA in Finland has declined during this millennium. At the same time the incidence of all disability pensions in the Finnish population has remained stable. The reason for this favourable development could not be solved by this study, but it has occurred in parallel with increasingly active treatment strategies used for early RA, as well as with altered legislation prioritizing vocational rehabilitation over permanent WD pension.

The rates of permanent WD in earlier cohorts of RA patients have been approximately 20 % after 2 years, and 50 % after 5 years of RA (Verstappen et al. 2004), higher in European studies (Doeglas et al. 1995, Mau et al. 1996, Fex et al. 1998, van Jaarsveld et al. 1998, Albers et al. 1999, Barrett et al. 2000, Chorus et al. 2000, Young et al. 2002, Mau et al. 2005, Björk et al. 2009) than in North-American ones (Mitchell et al. 1988, Yelin 1992, Wolfe et al. 2007a, Allaire et al. 2008a). In Finland the incidence of WD in the 1980s was 40% in the patients after 5 years of RA duration, 50 % after 10 years, and 67 % after 15 years of RA (Mäkisara and Mäkisara 1982). Younger age, light work, extensive education and vocational training significantly protected the patients' working ability. Nissilä and co-workers studied prospectively another Finnish cohort of 107 patients with recent RA, starting from the 1970s' and found that after 3 years' disease duration 32 % of the patients were permanently work disabled due to their disease (Nissilä et al. 1983). In a follow-up study of the aforementioned material, Kaarela et al. found that 43 % of the patients had retired due to RA by the 8-year follow-up visit, 7 % due to other diseases and 8 % had limited work capacity (Kaarela et al. 1987). Strenuous work, higher age and severe RA were associated with work disability. Further, on the same Heinola Follow-up Survey, Jäntti and colleagues published the 20 year follow-up data and found the incidence of work disability by that time to be 80 % (Jäntti et al. 1999). Sokka et al. studied prospectively a cohort of 86 gainfully employed patients with early RA diagnosed during the 1980s (Sokka et al. 1999a). Two years after the disease onset 23 % of the patients had retired due to RA, and 10 years after the diagnosis 38 % of the patients had become work disabled. The fastest decline in the loss of working ability took place during the first 2 years. In the Cox regression

analysis, baseline risk factors for later work disability were a physically demanding job, higher age and higher number of swollen joints.

In addition to the disease-dependent factors, the national differences in social security systems play an important role in explaining the different rates of WD in RA. Chung et al. compared a Finnish cohort of 364 working aged and working RA patients to a US cohort of 269 similar RA patients and found the probability to continue working 1, 2, 3 and 4 years after the RA diagnosis to be 92 %, 86 %, 84 % and 80 % in Finland and 92 %, 89 %, 89 % and 84 % in the US, respectively (Chung et al. 2006). The figures were thus lower than in previous studies, but still, after adjustment, 2.6-fold higher in Finland than in the US, even though the Finnish RA patients had better functional capacity and global status as well as less pain than the US patients. In the US, only clearly elevated pain score or patients global assessment at baseline and non-Caucasian race were risk factors for work disability, while in Finland higher age, non-sedentary work, lower education, use of methotrexate or prednisolone, as well as elevated pain, fatigue and global assessment scores and MHAQ at follow-up were associated with an increased risk for work disability. Similar differences between countries were found in the Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) trial, where the authors collected cross-sectional data of 8039 RA patients from 32 countries (Sokka et al. 2010). In this study, 37 % of the patients who had been working at the time of the first symptoms of RA reported subsequent work disability due to RA. When the 1756 patients with the disease onset during this millennium were analysed separately, the authors found the probabilities to continue working to be 80 % after 2 years of RA and 68 % after 5 years, similarly in high gross domestic product (GDP) (>24K US dollars [USD] per capita) and low-GDP (<11K USD per

capita) countries. Patients who stopped working had worse clinical status than the ones who continued to work, in both the high- and the low-GDP countries, with the HAQ-score as the one most important identifier of work disability. Most interestingly, the patients who had become work disabled in the high-GDP countries had significantly better HAQ and DAS28 scores than the patients who continued to work in the low-GDP countries, again stressing the importance of different social security systems' explanatory role.

In a more recent US study, Allaire and colleagues assessed data of 5384 RA patients with a mean disease duration of 14 years form a large national databank between 2002-05 (Allaire et al. 2008a). Of these patients 4385 had been employed at disease onset. The prevalence of arthritis-attributed work cessation was 13.6 % in subjects with 1-3 years of disease duration, increasing to 19.0 %, 28.9 %, 28.3%, 38.2 % and 42.2 % after a disease duration of 4-6, 9-11, 14-16, 19-21 and ≥25 years, respectively. On the other hand, 39 % of the patients who had stopped working at some time, returned later to work at least temporarily. Thus, RA still causes a notable menace to the patient's working ability, but the contemporary risk may be lower than that in the previous decades.

In the most recent large Swedish study, Neovius and colleagues described the annual sick leave days during four years before and after the diagnosis for a register-based cohort of 3029 working-aged early RA patients diagnosed 1999-2007, and compared them to a matched general population. The authors found that sick leaves increased steadily during the preceding year before RA diagnosis peaking to 147 days/year during the year after the diagnosis. After that the days on sick leave decreased while the days on disability pension increased, and a steady 19 % of the patients received sickness benefits for 365 days/year 1-4 years after the RA

diagnosis. Nevertheless, the annual WD days in these Swedish cohorts were 2-4 times higher than in the current Finnish cohorts, and the proportion of patients not utilizing sick leave was lower than in our cohort. This may partly be explained by different criteria for sickness benefits even in the Nordic countries (Hytti 2008, Virjo 2008). In the Swedish study patients diagnosed in 1999 and in 2003 had a higher increase in days on sick leave or disability pension from the year preceding the diagnosis to the year after the diagnosis than the patients diagnosed in 2007; however, there was a similar trend in the general population reflecting a possible change in the society (Neovius et al. 2011b).

Further, Ziegler et al. elucidated the trends in treatments and outcomes of 38 723 German patients with established RA between 1997-2007 (Ziegler et al. 2010). They found that throughout the follow-up, in parallel with increasingly active treatments and better clinical outcomes, the proportion of patients requiring at least one sick-leave during the preceding year had decreased from 39 % to 27 %, and at the same time the mean duration of sick-leaves had declined from 71 to 33 days. Similarly, the proportion of those employed of all working aged patients increased from 37 % to 46 % in women and from 47 % to 57 % in men. The age and sex standardised increase in the employment rates was 7 %, but during the same follow-up time also the employment rate of the general population improved making the interpretation of the results somewhat complicated.

Clearly, compared to the earlier Finnish results (Mäkisara and Mäkisara 1982, Nissilä et al. 1983, Kaarela et al. 1987, Jäntti et al. 1999, Sokka et al. 1999a, Chung et al. 2006), but even to the most recent European (Ziegler et al. 2010, Neovius et al. 2011b) and US (Allaire et al. 2008a) ones, the incidence of continuous WD during the first 2 years after the diagnosis found in the present study was significantly

lower, resembling that found in the FIN-RACo study (Puolakka et al. 2004); as the percentage of continuously work disabled patients at 2 years after the diagnosis was 8.9 % for the first cohort, and as low as 4.8 % for the last cohort. Since the treatment strategies during the same time had become increasingly active, it would be tempting to claim that the decline in WD could be accredited to the aggressive treatments. Nonetheless, undoubtedly due to a channelling bias, the patients with the less effective initial treatment, i.e. single non-MTX DMARD, had a lower risk of WD than the patients initially treated more actively. Still, evidently in the scale of clinical disease activity in early RA, the patients with a mild RA, and therefore the best prognosis to start with, are the ones prescribed the mildest treatments. And the patients receiving more aggressive treatments are the ones with an active disease and thus an unfavourable consequent working ability scenario (Chung et al. 2006). Probably, still, had these patients been treated with less effective strategies, their WD rates would be higher.

Thus far the studies proving a certain traditional DMARD treatment to protect the RA patients' working ability are sparse. In 1991, in a Scandinavian multi-centre study Borg et al. showed, that early RA patients treated double-blindly with auranofin had by 24 months a higher probability of continuing to work than those treated with placebo (Borg et al. 1991). Within the FIN-RACo trial, Puolakka and others found that the patients initially treated with the FIN-RACo strategy had less sick leave days than the patients treated with the SINGLE strategy and a smaller proportion of patients receiving a permanent disability pension by 5 years, even though after adjustment the latter difference was not statistically significant (Puolakka et al. 2004). However, none of the patients achieving remission at 6 months became work disabled during 5 years (Puolakka et al. 2005a). In the 2-year

analysis of the BeSt study the mean worked hours per week were higher in both of the initial combination groups than in the sequential monotherapy or the step-up combination therapy groups (van den Hout et al. 2009).

Regardless of the channelling bias discussed above, in the present study adalimumab and etanercept appeared to protect the patients' working ability. Nonetheless, they were used infrequently, and started first after a few years from the diagnosis, thus the use of these biologics may, at best, explain but a very small part of the total decline of continuous WD in RA. The role of infliximab in this respect is unfortunately unclear, as the data of its use is not included in the present analysis. However, as all the biologics were, after their introduction, thus during the follow-up of the present study, first reserved for RA patients with treatment-resistant and usually longstanding disease, their use in early RA would have been exceptional and thus cannot explain the current declining trend of WD in Finland. From other studies the effect of biologics on WD is still unclear in established RA (Yelin et al. 2003, Wolfe et al. 2007a, Allaire et al. 2008b, Halpern et al. 2009, Augustsson et al. 2010, Verstappen et al. 2010), as well as in early disease (Smolen et al. 2006, Bejarano et al. 2008).

Another possible explanation for the declining trend in continuous WD is the altered legislation (Cooke 2006). In Finland, the legislation was reformed in 2004 prioritizing vocational rehabilitation over WD pension, and transferring the responsibility of its organisation to the pension providers. While this may have affected the WD pension rates in RA patients, the rate of WD pensions in the general population have remained at a similar level throughout the follow-up, and the SIR for a premature disability pension in the early RA patients compared to the general Finnish population has declined during the follow-up. The current 3-fold

risk of premature early RA dependent disability pension found in this study is also remarkably lower than the 4-7-fold risk (van Jaarsveld et al. 1998, Albers et al. 1999), not to mention the 32-fold risk (Barrett et al. 2000), found in earlier studies.

Worth noting is, that even though the altered legislation may have prevented certain work disabled patients from receiving permanent WD pensions, these same patients would still have received temporary rehabilitation allowances, which, if still continuing at the end of our follow-up period, were also registered in our data as continuous WD. Thus, the diminishing proportion of early RA patients becoming work disabled under the recent years appears to represent a factual phenomenon of a better preserved working capacity, rather than a consequence of a redefinition of WD. During the first year after the diagnosis the great majority of the WD days were caused either by short- or by long-term sick-leaves (Puolakka et al. 2006), as, according to the Finnish system, persons unable to perform their usual tasks will first be paid a sickness allowance for up to 150 working days, then a rehabilitation allowance, and after that, at the earliest after one year of sick leave or rehabilitation allowance, a permanent disability pension. During the first year after the RA diagnosis the mean number of annual WD days was similar in all year cohorts, but during the second year after the diagnosis, when the majority of sick-leave days are dependent on long-term WD, the latest year cohort had a significantly lower mean number of annual WD days per patient years than the preceding year cohorts, a fact confirming the accuracy of the difference noted between the cohorts in continuous WD.

The patient dependent factors behind the observed trend in WD could not be analyzed, as the data on clinical disease activity and radiographic changes was lacking, as well as that on employment and schooling details of the patients.

However, earlier studies have shown that the most important patient depending factors predicting WD are severe and long-standing RA, reduced functional ability, physically demanding work and older age (Verstappen et al. 2004), the latter confirmed also in the present study. Interestingly, male patients were found to have a clearly higher risk of RA related WD than females. In the FIN-RACo study, after 5 years females had a slightly higher risk for WD compared to males (Puolakka et al. 2006), another study had similar findings (Kaptein et al. 2009). On the other hand, another study found a slightly increased risk for arthritis related WD in males (Badley and Wang 2001), while others have found no gender-association (Doeglas et al. 1995, Albers et al. 1999, Puolakka et al. 2005b, Allaire et al. 2009). According to Statistics Finland, 70 % of the Finnish working aged males and 71 % of females participated to labour force in 2008, thus a higher engagement to housekeeping and lesser to paid employment does not explain the lower risk for disability pensions in females compared to males. Nevertheless, it is possible that male workers are more often occupied in manual labour than female workers and therefore become more often work disabled.

To conclude, the results of this study demonstrate that it is possible to decrease or to postpone long-term WD in patients with early RA. At the same time with this development the treatments used in early RA have become increasingly active. TNF-inhibitors contribute to preserving the patients' working ability, but their use explains but a minor part of the current favourable outcome. A part of the declining incidence of continuous WD in early RA may be explained by legislative changes emphasizing vocational rehabilitation, however, these alterations do not appear to have affected the incidence of premature permanent WD in the total Finnish population and the standardised incidence ratio of RA dependent permanent WD has

decreased during this millennium. It is also possible, that the contemporary, active possibilities to treat RA towards better outcomes, have changed both the patients' and the physicians' attitudes towards the more favourable prognosis of the disease. Permanent WD has ceased to be a self-evident consequence of RA.

SUMMARY AND CONCLUSIONS

1. Using tight clinical controls and targeting in remission results in good functional and clinical outcomes in most RA patients even in long-term. Initial therapy with a combination of DMARDs in early RA results in higher rates of patients achieving strict ACR remission even after 11 years of disease duration than initial single-DMARD therapy.

2. Aiming at remission and using tight clinical controls and intraarticular GC injections results in low long-term radiological progression in the hand and feet joints, as well as in the large joints in most RA patients. Patients treated initially with a combination of DMARDs have less long-term radiological damage than those treated initially with DMARD monotherapy. Early remission predicts slow radiographic progression.

3. During the present millennium more and more active drug treatments have been taken into practice in Finland. Currently, combination therapy including methotrexate is the most commonly prescribed treatment strategy for early RA. Less than 5 % of the patients are not using DMARDs within the first 3 months after diagnosis.

4. In parallel with the increasingly active treatment strategies, continuous work disability in early RA has declined in Finland. Other possible explanations for this evolution are the changed legislation prioritizing vocational rehabilitation over disability pension as well as altered attitudes towards the more favourable prognosis of RA due to contemporary active treatment strategies.

ACKNOWLEDGEMENTS

This study was carried out at the Department of Internal Medicine, Tampere University Hospital, and at the School of Medicine, University of Tampere, Finland.

I am truly grateful to Jukka Mustonen, the professor of Internal Medicine, for the opportunity and encouragement for the current research. I also convey a warm and sincere admiration for his continuing boyish enthusiasm towards science and literature, as well as for his inspiring example of not being afraid of anything or anybody.

I express my deep gratitude to the head of department, docent Kari Pietilä, for not only ensuring me the most flexible opportunities to take time off work to accomplish the current study, but also for being an excellent boss who gives his staff a feeling of being on their side. All of the above applies also for docent Jaakko Antonen, who was a great stand-in boss earlier on, and an understanding maker of the on-call schedules after that. In addition to his administrative skills he is an experienced rheumatologist and clinician from whom I have learned a lot.

I would like to heartily thank my closest boss and my closest supervisor, docent Markku Korpela, for trusting me with this extraordinary opportunity to do research that really matters, and to collaborate with all the leading Finnish rheumatologists. He has, despite his many duties, always found the time to provide relevant, yet friendly and encouraging comments on my scientific efforts. Moreover, he has taught me all I know about rheumatology, and given me a shining example of how to boldly apply the latest study results into everyday clinical practice. He is also to be thanked for maintaining balanced and fair working conditions for all the employees in the Centre for Rheumatology.

I believe that I would never have become a rheumatologist had I not, during the last years of my residency for internal medicine, had the chance to hear my other supervisor for this project, professor Timo Möttönen, give an inspiring presentation about the FIN-RACo trial. His charismatic example opened my eyes to the fact that rheumatology could, in fact, be exciting and full of opportunities and hope. The Finnish RA patients are in great debt for him for starting the FIN-RACo project, which has revolutionized the RA treatment in Finland and thus changed the life of many. I am extremely grateful for him for allowing me to continue this part of his life work, as well as for all the expertise and help he has offered me during this task.

Working with our brilliant statistician, Hannu Kautiainen, has been an epic privilege. Despite the five-hour round-drives to Äänekoski, the statistical sessions in the Medcare premises have never felt like work, but have been moments full of inspiration, wit, and humour. I sincerely hope to be able to continue working with Hannu a long time in the future, and I am indescribably thankful for all the doors this collaboration has opened me thus far. Besides me, the whole research community of Finnish rheumatology owes him a great deal for his giant contribution.

With all the inspiration, wit, and humour, the statistical sessions in Äänekoski might have gotten out of hand, had the voice of reason, Salme Järvenpää, not been present. I am deeply grateful for all her statistical expertise combined with her perfect common sense, which has kept us on the right track. Moreover, not only me, but everybody depending on the statistical help of the Medcare Foundation are indebted to the irreplaceable Pia Jauhiainen, whose preciseness and authority guarantee that every single piece of data is exactly as it should.

This thesis could not have been completed without the dedicated help of docent Kari Puolakka, who, besides being an essential participant of the FIN-RACo study group, is the cornerstone of the cooperation with the Social Institute of Insurance, on which half of this thesis is based on. I am thus doubly indebted to him, first for giving fast and constructive comments on the FIN-RACo part of the study, and secondly and more importantly, for involving me, out of all people, in this formidable, enviable database of Finnish early RA patients.

I am extremely grateful for the opportunity of collaborating with professor Marjatta Leirisalo-Repo. Her fast and apt remarks have been of great help in finalising the manuscripts. In general, I admire her active mind and her openness to new ideas. I have also felt exceedingly honoured for the way she has introduced me to her international contacts and involved me in her other projects.

Anyone having talked with professor Pekka Hannonen can easily believe the rumours that he, in fact, is the brain behind the FIN-RACo trial. His sharp mind gets right to the point, yet his broad education allows him to express himself in a sophisticated manner, and I am much obliged to him for all his help.

Working with the fair and friendly professor Markku Hakala has been a great privilege. Professor Leena Laasonen owns my deep gratitude for her fast and precise analysis of the radiographs and prompt answer to my questions. I am grateful to Harri Blåfield, MD, for his participation in the FIN-RACo Trial and would like to acknowledge his exemplary preciseness in fulfilling the study forms. I heartily thank Anna Karjalainen, MD, PhD, Heikki Julkunen, MD, PhD, and Riitta Luosujärvi, MD, PhD, for their collaboration in the preparation of the manuscripts. Most importantly, this study could not have been carried out without the contribution of all the other physicians and nurses of the FIN-RACo Trial, and I am truly grateful for each and every one of them. Further, all the patients having had the guts to leap in the dark and participate in the FIN-RACo Trial deserve thanks.

I am exceedingly obliged to Lauri Virta MD, PhD, and to Timo Pohjolainen, MD, PhD, for their great expertise in the complex world of social security and services, and for their endless patience when explaining them to me.

The comments docent Jukka Martio and docent Pekka Kurki gave on my work were of great importance for finishing this thesis and I am deeply grateful for their patience and expertise.

I thank docent Ole Wirta and professor emeritus Amos Pasternack for introducing me to the world of science, and apologize to them for not being interested enough in the complications of type 2 diabetes. Similarly, I would like to send my warm thoughts to docents Jaana Syrjänen and Satu Mäkelä; sharing the study room with these brilliant ladies during my earlier effort of a scientific career was great and inspiring fun, but did indeed reveal my limited concentration skills.

I am thankful to all the members of my work communities for their supportive attitudes, especially to my Mänttä boss, Ismo Pirttiniemi, MD, for trusting me to organize my tasks freely, and to my colleague, Susanna Sihvonen, MD, PhD, for filling in for me while I spent months after months finishing this project. I am happy and grateful of the mere existence of my friend and colleague Heidi Mäkinen, MD, PhD, who has supported, inspired and entertained me in numerous ways. I also want to thank Tuulikki Sokka, MD, PhD, for demonstrating the achievements of endless energy and scientific brilliance, as well as for helping me behind the scenes on several occasions.

I want to thank all my friends, especially Minerva Krohn, and Tiina and Juha Vaitilo for being who they are, and for accepting me as I am, throughout the years. Also, the encouragement and practical advices given by my Facebook friends have been of utmost importance, even though their online company has sometimes been distractingly tempting with regard to this project.

Supposedly this is not the right occasion for expressing all the love and gratitude I feel for my parents, professors emerita Liisa and emeritus Kari Rantalaiho. So I just thank them for their endless and limitless support in whatever situation I might have faced. I also thank my sister, Taina, and my brothers, Petteri and Heikki, for being just the family I am proud of. I am most obliged to our trusted nanny, Elsa Laine, for taking care of my home and kids (and earlier on, me), thus guaranteeing me the freedom to concentrate on things I am better at.

Finally, my husband Matti and daughters Ilona and Onneli are the reason why I do anything. They have supported and comforted and loved me in all my ups and downs; shown me the true meaning of life. Had I not had this unbelievable luck of finding the absolute best man in the world, who then has given me these wonderful and amazing girls, I would probably have ended up a bitter bitch spending all my money and time on horses, and being at best a mediocre equestrian would really have achieved nothing in life. So thank you for everything, my loved ones, you make all the difference.

This work was financially supported by grants from the Competitive Research Funding of the Tampere University Hospital (Grants 9G174, 9L083, and 9M124), the Scandinavian Rheumatology Research Foundation, the Medcare Foundation, the Finnish Medical Society Duodecim, and Tampereen Reumayhdistys.

Tampere, 1st May 2012

Vappu Rantalaiho

REFERENCES

Abu-Shakra M, Toker R, Flusser D, Flusser G, Friger M, Sukenik S and Buskila D (1998). Clinical and radiographic outcomes of rheumatoid arthritis patients not treated with disease-modifying drugs. Arthritis Rheum 41: 1190-5.

Albers JM, Kuper HH, van Riel PL, Prevoo ML, van 't Hof MA, van Gestel AM and Severens JL (1999). Socio-economic consequences of rheumatoid arthritis in the first years of the disease. Rheumatology (Oxford) 38: 423-30.

Albers JM, Paimela L, Kurki P, Eberhardt KB, Emery P, van 't Hof MA, Schreuder FH, Leirisalo-Repo M and van Riel PL (2001). Treatment strategy, disease activity, and outcome in four cohorts of patients with early rheumatoid arthritis. Ann Rheum Dis 60: 453-8.

Aletaha D and Smolen JS (2002). The rheumatoid arthritis patient in the clinic: comparing more than 1,300 consecutive DMARD courses. Rheumatology (Oxford) 41: 1367-74.

Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Menard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovsky J, Wolfe F and Hawker G (2010). 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 62: 2569-81.

Allaire S, Wolfe F, Niu J and Lavalley MP (2008a). Contemporary prevalence and incidence of work disability associated with rheumatoid arthritis in the US. Arthritis Rheum 59: 474-80.

Allaire S, Wolfe F, Niu J, Zhang Y, Zhang B and LaValley M (2008b). Evaluation of the effect of anti-tumor necrosis factor agent use on rheumatoid arthritis work disability: the jury is still out. Arthritis Rheum 59: 1082-9.

Allaire S, Wolfe F, Niu J, LaValley MP, Zhang B and Reisine S (2009). Current risk factors for work disability associated with rheumatoid arthritis: recent data from a US national cohort. Arthritis Rheum 61: 321-8.

Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS and et al. (1988). The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31: 315-24.

Augustsson J, Neovius M, Cullinane-Carli C, Eksborg S and van Vollenhoven RF (2010). Patients with rheumatoid arthritis treated with tumour necrosis factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry). Ann Rheum Dis 69: 126-31.

Badley EM and Wang PP (2001). The contribution of arthritis and arthritis disability to nonparticipation in the labor force: a Canadian example. J Rheumatol 28: 1077-82.

Bakker MF, Jacobs JW, Welsing PM, van der Werf JH, Linn-Rasker SP, van der Veen MJ, Lafeber FP and Bijlsma JW (2010). Are switches from oral to subcutaneous methotrexate or addition of ciclosporin to methotrexate useful steps in a tight control treatment strategy for rheumatoid arthritis? A post hoc analysis of the CAMERA study. Ann Rheum Dis 69: 1849-52.

Bakker MF, Jacobs JW, Welsing PM, Vreugdenhil SA, van Booma-Frankfort C, Linn-Rasker SP, Ton E, Lafeber FP and Bijlsma JW (2011). Early clinical response to treatment predicts 5-year outcome in RA patients: follow-up results from the CAMERA study. Ann Rheum Dis.

Barrett EM, Scott DG, Wiles NJ and Symmons DP (2000). The impact of rheumatoid arthritis on employment status in the early years of disease: a UK community-based study. Rheumatology (Oxford) 39: 1403-9.

Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Genovese MC, Wasko MC, Moreland LW, Weaver AL, Markenson J and Finck BK (2000). A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 343: 1586-93.

Behrens F, Koehm M and Burkhardt H (2011). Update 2011: leflunomide in rheumatoid arthritis - strengths and weaknesses. Curr Opin Rheumatol 23: 282-7.

Bejarano V, Quinn M, Conaghan PG, Reece R, Keenan AM, Walker D, Gough A, Green M, McGonagle D, Adebajo A, Jarrett S, Doherty S, Hordon L, Melsom R, Unnebrink K, Kupper H and Emery P (2008). Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. Arthritis Rheum 59: 1467-74.

Bendtzen K, Geborek P, Svenson M, Larsson L, Kapetanovic MC and Saxne T (2006). Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab. Arthritis Rheum 54: 3782-9.

Berard A, Solomon DH and Avorn J (2000). Patterns of drug use in rheumatoid arthritis. J Rheumatol 27: 1648-55.

Björk M, Thyberg I, Rikner K, Balogh I and Gerdle B (2009). Sick leave before and after diagnosis of rheumatoid arthritis--a report from the Swedish TIRA project. J Rheumatol 36: 1170-9.

Bluestone R (1970). Rheumatoid arthritis. Medical management. Br Med J 4: 602-4.

Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, van Zeben D, Dijkmans BA, Peeters AJ, Jacobs P, van den Brink HR, Schouten HJ, van der Heijde DM, Boonen A and van der Linden S (1997). Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 350: 309-18.

Borg G, Allander E, Berg E, Brodin U, From A and Trang L (1991). Auranofin treatment in early rheumatoid arthritis may postpone early retirement. Results from a 2-year double blind trial. J Rheumatol 18: 1015-20.

Borigini MJ and Paulus HE (1995). Innovative treatment approaches for rheumatoid arthritis. Combination therapy. Baillieres Clin Rheumatol 9: 689-710.

Bosello S, Fedele AL, Peluso G, Gremese E, Tolusso B and Ferraccioli G (2011). Very early rheumatoid arthritis is the major predictor of major outcomes: clinical ACR remission and radiographic non-progression. Ann Rheum Dis 70: 1292-5.

Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL and Spencer-Green GT (2006). The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 54: 26-37.

Briggs AM, March L, Lassere M, Reid C, Henderson L, Murphy B, van den Haak R, Rischin A, Staples M and Buchbinder R (2009). Baseline comorbidities in a population-based cohort of rheumatoid arthritis patients receiving biological therapy: data from the Australian rheumatology association database. Int J Rheumatol 2009: 861481.

Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, Hensor E, Wakefield RJ, O'Connor PJ and Emery P (2008). An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 58: 2958-67.

Bruce B and Fries JF (2003). The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol 30: 167-78.

Bruynesteyn K, van der Heijde D, Boers M, Saudan A, Peloso P, Paulus H, Houben H, Griffiths B, Edmonds J, Bresnihan B, Boonen A and van der Linden S (2002). Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum 46: 913-20.

Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dorner T, Ferraccioli G, Gottenberg JE, Isaacs J, Kvien TK, Mariette X, Martin-Mola E, Pavelka K, Tak PP, van der Heijde D, van Vollenhoven RF and Emery P (2011). Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 70: 909-20.

Bukhari M, Lunt M, Harrison BJ, Scott DG, Symmons DP and Silman AJ (2002). Rheumatoid factor is the major predictor of increasing severity of radiographic erosions in rheumatoid arthritis: results from the Norfolk Arthritis Register Study, a large inception cohort. Arthritis Rheum 46: 906-12.

Bukhari M, Thomson W, Naseem H, Bunn D, Silman A, Symmons D and Barton A (2007). The performance of anti-cyclic citrullinated peptide antibodies in predicting the severity of radiologic damage in inflammatory polyarthritis: results from the Norfolk Arthritis Register. Arthritis Rheum 56: 2929-35.

Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B, Khraishi M, Leclercq SA, Legare J, Mosher DP, Pencharz J, Pope JE, Thomson J, Thorne C, Zummer M and Bombardier C (2011). Canadian Rheumatology Association Recommendations for Pharmacological Management of Rheumatoid Arthritis with Traditional and Biologic Disease-modifying Antirheumatic Drugs. J Rheumatol.

Calguneri M, Pay S, Caliskaner Z, Apras S, Kiraz S, Ertenli I and Cobankara V (1999). Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. Clin Exp Rheumatol 17: 699-704.

Capell HA, Madhok R, Porter DR, Munro RA, McInnes IB, Hunter JA, Steven M, Zoma A, Morrison E, Sambrook M, Wui Poon F, Hampson R, McDonald F, Tierney A, Henderson N and Ford I (2007). Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from the double-blind placebo-controlled MASCOT study. Ann Rheum Dis 66: 235-41.

Carli C, Ehlin AG, Klareskog L, Lindblad S and Montgomery SM (2006). Trends in disease modifying antirheumatic drug prescription in early rheumatoid arthritis are influenced more by hospital setting than patient or disease characteristics. Ann Rheum Dis 65: 1102-5.

Chan ES and Cronstein BN (2010). Methotrexate--how does it really work? Nat Rev Rheumatol 6: 175-8.

Choi HK, Hernan MA, Seeger JD, Robins JM and Wolfe F (2002). Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet 359: 1173-7.

Chorus AM, Miedema HS, Wevers CJ and van Der Linden S (2000). Labour force participation among patients with rheumatoid arthritis. Ann Rheum Dis 59: 549-54.

Choy EH, Smith CM, Farewell V, Walker D, Hassell A, Chau L and Scott DL (2008). Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. Ann Rheum Dis 67: 656-63.

Chung CP, Sokka T, Arbogast PG and Pincus T (2006). Work disability in early rheumatoid arthritis: higher rates but better clinical status in Finland compared with the US. Ann Rheum Dis 65: 1653-7.

Cohen S, Cannon GW, Schiff M, Weaver A, Fox R, Olsen N, Furst D, Sharp J, Moreland L, Caldwell J, Kaine J and Strand V (2001). Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group. Arthritis Rheum 44: 1984-92.

Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, Kremer J, Bear MB, Rich WJ and McCabe D (2002). Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 46: 614-24.

Cooke M (2006). Policy changes and the labour force participation of older workers: evidence from six countries. Can J Aging 25: 387-400.

Corbett M, Dalton S, Young A, Silman A and Shipley M (1993). Factors predicting death, survival and functional outcome in a prospective study of early rheumatoid disease over fifteen years. Br J Rheumatol 32: 717-23.

Current Care Guideline (2009). Rheumatoid arthritis (online). Working group set up by the Finnish Medical Society Duodecim and the Finnish Society for Rheumatology. Available on internet: www.kaypahoito.fi.

Cush JJ (2007). Early rheumatoid arthritis -- is there a window of opportunity? J Rheumatol Suppl 80: 1-7.

Da Silva JA, Jacobs JW, Kirwan JR, Boers M, Saag KG, Ines LB, de Koning EJ, Buttgereit F, Cutolo M, Capell H, Rau R and Bijlsma JW (2006). Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis 65: 285-93.

Detert J, Pischon N, Burmester GR and Buttgereit F (2010). The association between rheumatoid arthritis and periodontal disease. Arthritis Res Ther 12: 218.

Doeglas D, Suurmeijer T, Krol B, Sanderman R, van Leeuwen M and van Rijswijk M (1995). Work disability in early rheumatoid arthritis. Ann Rheum Dis 54: 455-60.

Donahue KE, Gartlehner G, Jonas DE, Lux LJ, Thieda P, Jonas BL, Hansen RA, Morgan LC and Lohr KN (2008). Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. Ann Intern Med 148: 124-34.

Doran MF, Pond GR, Crowson CS, O'Fallon WM and Gabriel SE (2002). Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. Arthritis Rheum 46: 625-31.

Dougados M, Combe B, Cantagrel A, Goupille P, Olive P, Schattenkirchner M, Meusser S, Paimela L, Rau R, Zeidler H, Leirisalo-Repo M and Peldan K (1999). Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Ann Rheum Dis 58: 220-5.

Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC and Hazes JM (1999). Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. Arthritis Rheum 42: 1854-60.

Drossaers-Bakker KW, Kroon HM, Zwinderman AH, Breedveld FC and Hazes JM (2000). Radiographic damage of large joints in long-term rheumatoid arthritis and its relation to function. Rheumatology (Oxford) 39: 998-1003.

Drossaers-Bakker KW, Zwinderman AH, Vlieland TP, Van Zeben D, Vos K, Breedveld FC and Hazes JM (2002). Long-term outcome in rheumatoid arthritis: a simple algorithm of baseline parameters can predict radiographic damage, disability, and disease course at 12-year followup. Arthritis Rheum 47: 383-90.

Edwards CJ, Arden NK, Fisher D, Saperia JC, Reading I, Van Staa TP and Cooper C (2005). The changing use of disease-modifying anti-rheumatic drugs in individuals with rheumatoid arthritis from the United Kingdom General Practice Research Database. Rheumatology (Oxford) 44: 1394-8.

Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, Singh A, Pedersen RD, Koenig AS and Freundlich B (2008). Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 372: 375-82.

Faarvang KL, Egsmose C, Kryger P, Podenphant J, Ingeman-Nielsen M and Hansen TM (1993). Hydroxychloroquine and sulphasalazine alone and in combination in rheumatoid arthritis: a randomised double blind trial. Ann Rheum Dis 52: 711-5.

Farragher TM, Lunt M, Bunn DK, Silman AJ and Symmons DP (2007). Early functional disability predicts both all-cause and cardiovascular mortality in people with inflammatory polyarthritis: results from the Norfolk Arthritis Register. Ann Rheum Dis 66: 486-92.

Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, Furst D, Goldsmith C, Kieszak S, Lightfoot R and et al. (1993). The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum 36: 729-40.

Felson DT, Anderson JJ and Meenan RF (1994). The efficacy and toxicity of combination therapy in rheumatoid arthritis. A meta-analysis. Arthritis Rheum 37: 1487-91.

Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, Aletaha D, Allaart CF, Bathon J, Bombardieri S, Brooks P, Brown A, Matucci-Cerinic M, Choi H, Combe B, de Wit M, Dougados M, Emery P, Furst D, Gomez-Reino J, Hawker G, Keystone E, Khanna D, Kirwan J, Kvien TK, Landewe R, Listing J, Michaud K, Martin-Mola E, Montie P, Pincus T, Richards P, Siegel JN, Simon LS, Sokka T, Strand V, Tugwell P, Tyndall A, van der Heijde D, Verstappen S, White B, Wolfe F, Zink A and Boers M (2011). American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 63: 573-86.

Fex E, Larsson BM, Nived K and Eberhardt K (1998). Effect of rheumatoid arthritis on work status and social and leisure time activities in patients followed 8 years from onset. J Rheumatol 25: 44-50.

Finckh A, Liang MH, van Herckenrode CM and de Pablo P (2006a). Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. Arthritis Rheum 55: 864-72.

Finckh A, Choi HK and Wolfe F (2006b). Progression of radiographic joint damage in different eras: trends towards milder disease in rheumatoid arthritis are attributable to improved treatment. Ann Rheum Dis 65: 1192-7.

Finckh A (2009). Early inflammatory arthritis versus rheumatoid arthritis. Curr Opin Rheumatol 21: 118-23.

Firestein GS (2005). Immunologic mechanisms in the pathogenesis of rheumatoid arthritis. J Clin Rheumatol 11: S39-44.

Fraenkel L, Rabidou N and Dhar R (2006). Are rheumatologists' treatment decisions influenced by patients' age? Rheumatology (Oxford) 45: 1555-7.

Fries JF, Spitz P, Kraines RG and Holman HR (1980). Measurement of patient outcome in arthritis. Arthritis Rheum 23: 137-45.

Fries JF (1990). Reevaluating the therapeutic approach to rheumatoid arthritis: the "sawtooth" strategy. J Rheumatol Suppl 22: 12-5.

Gabriel SE, Crowson CS, Kremers HM, Doran MF, Turesson C, O'Fallon WM and Matteson EL (2003). Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. Arthritis Rheum 48: 54-8.

Gabriel SE and Michaud K (2009). Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther 11: 229.

Gaujoux-Viala C, Smolen JS, Landewe R, Dougados M, Kvien TK, Mola EM, Scholte-Voshaar M, van Riel P and Gossec L (2010). Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 69: 1004-9.

Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Wasko MC, Moreland LW, Weaver AL, Markenson J, Cannon GW, Spencer-Green G and Finck BK (2002). Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum 46: 1443-50.

Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, Zwinderman AH, Ronday HK, Han KH, Westedt ML, Gerards AH, van Groenendael JH, Lems WF, van Krugten MV, Breedveld FC and Dijkmans BA (2005). Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 52: 3381-90.

Goodson N, Marks J, Lunt M and Symmons D (2005). Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. Ann Rheum Dis 64: 1595-601.

Gorter SL, Bijlsma JW, Cutolo M, Gomez-Reino J, Kouloumas M, Smolen JS and Landewe R (2010). Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 69: 1010-4.

Graudal N (2004). The natural history and prognosis of rheumatoid arthritis: association of radiographic outcome with process variables, joint motion and immune proteins. Scand J Rheumatol Suppl 118: 1-38.

Graudal N and Jurgens G (2010). Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomized placebo-controlled or drug-controlled studies, including 112 comparisons. Arthritis Rheum 62: 2852-63.

Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, Kincaid W and Porter D (2004). Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 364: 263-9.

Guillemin F, Billot L, Boini S, Gerard N, Odegaard S and Kvien TK (2005). Reproducibility and sensitivity to change of 5 methods for scoring hand radiographic damage in patients with rheumatoid arthritis. J Rheumatol 32: 778-86.

Haagsma CJ, van Riel PL, de Jong AJ and van de Putte LB (1997). Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. Br J Rheumatol 36: 1082-8.

Habib GS, Saliba W and Nashashibi M (2010). Local effects of intra-articular corticosteroids. Clin Rheumatol 29: 347-56.

Hafstrom I, Bala V, Albertsson K, Forslind K and Svensson B (2011). Joint destruction in early rheumatoid arthritis over 8 years is similar in women and men despite apparently higher disease activity and poorer function in women. Ann Rheum Dis 70: 709-10.

Hakala M, Nieminen P and Manelius J (1994). Joint impairment is strongly correlated with disability measured by self-report questionnaires. Functional status assessment of individuals with rheumatoid arthritis in a population based series. J Rheumatol 21: 64-9.

Halpern MT, Cifaldi MA and Kvien TK (2009). Impact of adalimumab on work participation in rheumatoid arthritis: comparison of an open-label extension study and a registry-based control group. Ann Rheum Dis 68: 930-7.

Hannonen P, Mottonen T, Hakola M and Oka M (1993). Sulfasalazine in early rheumatoid arthritis. A 48-week double-blind, prospective, placebo-controlled study. Arthritis Rheum 36: 1501-9.

Heliövaara M, Aho K, Aromaa A, Knekt P and Reunanen A (1993). Smoking and risk of rheumatoid arthritis. J Rheumatol 20: 1830-5.

Hetland ML, Stengaard-Pedersen K, Junker P, Lottenburger T, Ellingsen T, Andersen LS, Hansen I, Skjodt H, Pedersen JK, Lauridsen UB, Svendsen A, Tarp U, Podenphant J, Hansen G, Lindegaard H, de Carvalho A, Ostergaard M and Horslev-Petersen K (2006). Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis Rheum 54: 1401-9.

Hetland ML, Stengaard-Pedersen K, Junker P, Lottenburger T, Hansen I, Andersen LS, Tarp U, Svendsen A, Pedersen JK, Skjodt H, Lauridsen UB, Ellingsen T, van Overeem Hansen G, Lindegaard H, Vestergaard A, Jurik AG, Ostergaard M and Horslev-Petersen K (2008). Aggressive combination therapy with intraarticular glucocorticoid injections and conventional DMARDs in early rheumatoid arthritis: Second Year Clinical and Radiographic Results From The CIMESTRA Study. Ann Rheum Dis.

Hetland ML, Stengaard-Pedersen K, Junker P, Ostergaard M, Ejbjerg BJ, Jacobsen S, Lottenburger T, Hansen I, Tarp U, Andersen LS, Svendsen A, Pedersen JK, Lauridsen UB, Ellingsen T, Lindegaard H, Podenphant J, Vestergaard A, Jurik AG and Horslev-Petersen K (2010). Radiographic progression and remission rates in early rheumatoid arthritis - MRI bone oedema and anti-CCP predicted radiographic progression in the 5-year extension of the double-blind randomised CIMESTRA trial. Ann Rheum Dis 69: 1789-95.

Hider SL, Silman AJ, Thomson W, Lunt M, Bunn D and Symmons DP (2009). Can clinical factors at presentation be used to predict outcome of treatment with methotrexate in patients with early inflammatory polyarthritis? Ann Rheum Dis 68: 57-62.

Hoff M, Haugeberg G, Odegard S, Syversen S, Landewe R, van der Heijde D and Kvien TK (2009). Cortical hand bone loss after 1 year in early rheumatoid arthritis predicts radiographic hand joint damage at 5-year and 10-year follow-up. Ann Rheum Dis 68: 324-9.

Hyrich KL, Watson KD, Silman AJ and Symmons DP (2006). Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 45: 1558-65.

Hytti (2008). The Finnish employment and income security models in a Nordic comparison. [cited 9 June 2008]. Social Security and Health Research Working papers, 52. Available at: http://www.kela.fi/in/internet/liite.nsf/NET/100506142717EK/$File/Seloste52netti.pdf?OpenElement).

Isomäki H and Martio J (1976). [Medical treatment of rheumatoid arthritis]. Duodecim 92: 304-12.

Jacoby RK, Jayson MI and Cosh JA (1973). Onset, early stages, and prognosis of rheumatoid arthritis: a clinical study of 100 patients with 11-year follow-up. Br Med J 2: 96-100.

Jäntti J, Aho K, Kaarela K and Kautiainen H (1999). Work disability in an inception cohort of patients with seropositive rheumatoid arthritis: a 20 year study. Rheumatology (Oxford) 38: 1138-41.

Jäntti JK, Kaarela K, Belt EA and Kautiainen HJ (2002). Incidence of severe outcome in rheumatoid arthritis during 20 years. J Rheumatol 29: 688-92.

Jeurissen ME, Boerbooms AM, van de Putte LB, Doesburg WH, Mulder J, Rasker JJ, Kruijsen MW, Haverman JF, van Beusekom HJ, Muller WH and et al. (1991). Methotrexate versus azathioprine in the treatment of rheumatoid arthritis. A forty-eight-week randomized, double-blind trial. Arthritis Rheum 34: 961-72.

Jobanputra P, Wilson J, Douglas K and Burls A (2004). A survey of British rheumatologists' DMARD preferences for rheumatoid arthritis. Rheumatology (Oxford) 43: 206-10.

Kaarela K, Lehtinen K and Luukkainen R (1987). Work capacity of patients with inflammatory joint diseases. An eight-year follow-up study. Scand J Rheumatol 16: 403-6.

Kaarela K and Kautiainen H (1997). Continuous progression of radiological destruction in seropositive rheumatoid arthritis. J Rheumatol 24: 1285-7.

Kaipiainen-Seppänen O (2000). [Chronic arthritis in Finland]. Duodecim 116: 1445-51.

Kaipiainen-Seppänen O and Kautiainen H (2006). Declining trend in the incidence of rheumatoid factor-positive rheumatoid arthritis in Finland 1980-2000. J Rheumatol 33: 2132-8.

Kaiser R (2008). Incidence of lymphoma in patients with rheumatoid arthritis: a systematic review of the literature. Clin Lymphoma Myeloma 8: 87-93.

Kamin EJ and Multz CV (1969). Current therapy of rheumatoid arthritis. Calif Med 110: 17-23.

Kapetanovic M, Lindqvist E, Geborek P, Saxne T and Eberhard K (2011). Long-term mortality rate in rheumatoid arthritis patients with disease onset in the 1980s. Scand J Rheumatol 40: 433-8.

Kaptein SA, Gignac MA and Badley EM (2009). Differences in the workforce experiences of women and men with arthritis disability: a population health perspective. Arthritis Rheum 61: 605-13.

Karmakar S, Kay J and Gravallese EM (2010). Bone damage in rheumatoid arthritis: mechanistic insights and approaches to prevention. Rheum Dis Clin North Am 36: 385-404.

Katchamart W, Trudeau J, Phumethum V and Bombardier C (2009). Efficacy and toxicity of methotrexate (MTX) monotherapy versus MTX combination therapy with non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and meta-analysis. Ann Rheum Dis 68: 1105-12.

Kauppi MJ, Neva MH, Laiho K, Kautiainen H, Luukkainen R, Karjalainen A, Hannonen PJ, Leirisalo-Repo M, Korpela M, Ilva K and Mottonen T (2009). Rheumatoid atlantoaxial subluxation can be prevented by intensive use of traditional disease modifying antirheumatic drugs. J Rheumatol 36: 273-8.

Kean WF and Kean IR (2008). Clinical pharmacology of gold. Inflammopharmacology 16: 112-25.

Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, Fischkoff SA and Chartash EK (2004). Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 50: 1400-11.

Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, Pazdur J, Bae SC, Palmer W, Zrubek J, Wiekowski M, Visvanathan S, Wu Z and Rahman MU (2009). Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 68: 789-96.

Kiely PD, Brown AK, Edwards CJ, O'Reilly DT, Ostor AJ, Quinn M, Taggart A, Taylor PC, Wakefield RJ and Conaghan PG (2009a). Contemporary treatment principles for early rheumatoid arthritis: a consensus statement. Rheumatology (Oxford) 48: 765-72.

Kiely P, Williams R, Walsh D and Young A (2009b). Contemporary patterns of care and disease activity outcome in early rheumatoid arthritis: the ERAN cohort. Rheumatology (Oxford) 48: 57-60.

Kirwan JR (2001). Links between radiological change, disability, and pathology in rheumatoid arthritis. J Rheumatol 28: 881-6.

Kirwan JR, Bijlsma JW, Boers M and Shea BJ (2007). Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev: CD006356.

Kitahara K and Kawai S (2007). Cyclosporine and tacrolimus for the treatment of rheumatoid arthritis. Curr Opin Rheumatol 19: 238-45.

Kitas GD and Gabriel SE (2011). Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. Ann Rheum Dis 70: 8-14.

Klarenbeek NB, Guler-Yuksel M, van der Kooij SM, Han KH, Ronday HK, Kerstens PJ, Seys PE, Huizinga TW, Dijkmans BA and Allaart CF (2011). The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. Ann Rheum Dis 70: 1039-46.

Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, Ronnelid J, Harris HE, Ulfgren AK, Rantapaa-Dahlqvist S, Eklund A, Padyukov L and Alfredsson L (2006). A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 54: 38-46.

Knevel R, Schoels M, Huizinga TW, Aletaha D, Burmester GR, Combe B, Landewe RB, Smolen JS, Sokka T and van der Heijde DM (2010). Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 69: 987-94.

Korpela M, Laasonen L, Hannonen P, Kautiainen H, Leirisalo-Repo M, Hakala M, Paimela L, Blåfield H, Puolakka K and Möttönen T (2004). Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. Arthritis Rheum 50: 2072-81.

Kremer JM, Dougados M, Emery P, Durez P, Sibilia J, Shergy W, Steinfeld S, Tindall E, Becker JC, Li T, Nuamah IF, Aranda R and Moreland LW (2005). Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. Arthritis Rheum 52: 2263-71.

Krishnan E and Fries JF (2003). Reduction in long-term functional disability in rheumatoid arthritis from 1977 to 1998:a longitudinal study of 3035 patients. Am J Med 115: 371-6.

Kroot EJ, van Leeuwen MA, van Rijswijk MH, Prevoo ML, Van 't Hof MA, van De Putte LB and van Riel PL (2000). No increased mortality in patients with rheumatoid arthritis: up to 10 years of follow up from disease onset. Ann Rheum Dis 59: 954-8.

Kuper HH, van Leeuwen MA, van Riel PL, Prevoo ML, Houtman PM, Lolkema WF and van Rijswijk MH (1997). Radiographic damage in large joints in early rheumatoid arthritis: relationship with radiographic damage in hands and feet, disease activity, and physical disability. Br J Rheumatol 36: 855-60.

Kvalvik AG, Aadland HA, Hoyeraal HM and Larsen S (2001). Were the patterns of treatment for rheumatoid arthritis during 1977-1992 consistent with modern clinical guidelines? Scand J Rheumatol 30: 61-8.

Kvien TK, Scherer HU and Burmester GR (2009). Rheumatoid arthritis. EULAR Compendium on Rheumatic Diseases, BMJ Publishing Group and European League Against Rheumatism**:** 61-80.

Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, van Denderen JC, Westedt ML, Peeters AJ, Dijkmans BA, Jacobs P, Boonen A, van der Heijde DM and van der Linden S (2002). COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 46: 347-56.

Landewe RB (2010). Efficacy assessed in follow-ups of clinical trials: methodological conundrum. Arthritis Res Ther 12: 132.

Larsen A, Dale K and Eek M (1977). Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol Diagn (Stockh) 18: 481-91.

Leirisalo-Repo M, Kautiainen H and Laasonen L (2008). A randomized, doubleblinded, placebo-controlled study on addition of infliximab to the FIN-RACo DMARD combination therapy for initial six months in patients with early active rheumatoid arthritis. The NEO-RACo study [abstract]. Ann Rheum Dis 67.

Lindqvist E, Saxne T, Geborek P and Eberhardt K (2002). Ten year outcome in a cohort of patients with early rheumatoid arthritis: health status, disease process, and damage. Ann Rheum Dis 61: 1055-9.

Lindqvist E, Jonsson K, Saxne T and Eberhardt K (2003). Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. Ann Rheum Dis 62: 611-6.

Luukkainen R, Kajander A and Isomäki H (1977). Effect of gold on progression of erosions in rheumatoid arthritis. Better results with early treatment. Scand J Rheumatol 6: 189-92.

Maetzel A, Bombardier C, Strand V, Tugwell P and Wells G (1998). How Canadian and US rheumatologists treat moderate or aggressive rheumatoid arthritis: a survey. J Rheumatol 25: 2331-8.

Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M and Lipsky P (1999). Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 354: 1932-9.

Maravic M, Berge C, Daures JP and Boissier MC (2004). Survey of practices regarding management of early rheumatoid arthritis by rheumatologists in France. Clin Exp Rheumatol 22: 319-27.

Marchesoni A, Battafarano N, Arreghini M, Panni B, Gallazzi M and Tosi S (2003). Radiographic progression in early rheumatoid arthritis: a 12-month randomized controlled study comparing the combination of cyclosporin and methotrexate with methotrexate alone. Rheumatology (Oxford) 42: 1545-9.

Mau W, Bornmann M, Weber H, Weidemann HF, Hecker H and Raspe HH (1996). Prediction of permanent work disability in a follow-up study of early rheumatoid arthritis: results of a tree structured analysis using RECPAM. Br J Rheumatol 35: 652-9.

Mau W, Listing J, Huscher D, Zeidler H and Zink A (2005). Employment across chronic inflammatory rheumatic diseases and comparison with the general population. J Rheumatol 32: 721-8.

Mikuls TR and O'Dell J (2000). The changing face of rheumatoid arthritis therapy: results of serial surveys. Arthritis Rheum 43: 464-5.

Mikuls TR, Fay BT, Michaud K, Sayles H, Thiele GM, Caplan L, Johnson D, Richards JS, Kerr GS, Cannon GW and Reimold A (2011). Associations of disease activity and treatments with mortality in men with rheumatoid arthritis: results from the VARA registry. Rheumatology (Oxford) 50: 101-9.

Mitchell JM, Burkhauser RV and Pincus T (1988). The importance of age, education, and comorbidity in the substantial earnings losses of individuals with symmetric polyarthritis. Arthritis Rheum 31: 348-57.

Mustila A, Korpela M, Haapala AM, Kautiainen H, Laasonen L, Mottonen T, Leirisalo-Repo M, Ilonen J, Jarvenpaa S, Luukkainen R and Hannonen P (2011). Anti-citrullinated peptide antibodies and the progression of radiographic joint erosions in patients with early rheumatoid arthritis treated with FIN-RACo combination and single disease-modifying antirheumatic drug strategies. Clin Exp Rheumatol 29: 500-5.

Myasoedova E, Crowson CS, Kremers HM, Therneau TM and Gabriel SE (2010). Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum 62: 1576-82.

Mäkinen H, Kautiainen H, Hannonen P and Sokka T (2005a). Frequency of remissions in early rheumatoid arthritis defined by 3 sets of criteria. a 5-year followup study. J Rheumatol 32: 796-800.

Mäkinen H, Kautiainen H, Hannonen P and Sokka T (2005b). Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? Ann Rheum Dis 64: 1410-3.

Mäkinen H, Kautiainen H, Hannonen P, Möttönen T, Leirisalo-Repo M, Laasonen L, Korpela M, Blåfield H, Hakola M and Sokka T (2007). Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. J Rheumatol 34: 316-21.

Mäkisara GL and Mäkisara P (1982). Prognosis of functional capacity and work capacity in rheumatoid arthritis. Clin Rheumatol 1: 117-25.

Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, Laasonen L, Julkunen H, Luukkainen R, Vuori K, Paimela L, Blåfield H, Hakala M, Ilva K, Yli-Kerttula U, Puolakka K, Järvinen P, Hakola M, Piirainen H, Ahonen J, Pälvimaki I, Forsberg S, Koota K and Friman C (1999). Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 353: 1568-73.

Möttönen T, Hannonen P, Korpela M, Nissilä M, Kautiainen H, Ilonen J, Laasonen L, Kaipiainen-Seppänen O, Franzen P, Helve T, Koski J, Gripenberg-Gahmberg M, Myllykangas-Luosujarvi R and Leirisalo-Repo M (2002). Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. Arthritis Rheum 46: 894-8.

Neovius M, Simard JF and Askling J (2011a). Nationwide prevalence of rheumatoid arthritis and penetration of disease-modifying drugs in Sweden. Ann Rheum Dis 70: 624-9.

Neovius M, Simard JF and Askling J (2011b). How large are the productivity losses in contemporary patients with RA, and how soon in relation to diagnosis do they develop? Ann Rheum Dis 70: 1010-5.

Neva MH, Kauppi MJ, Kautiainen H, Luukkainen R, Hannonen P, Leirisalo-Repo M, Nissila M and Möttönen T (2000). Combination drug therapy retards the development of rheumatoid atlantoaxial subluxations. Arthritis Rheum 43: 2397-401.

NICE Clinical Guidelines (2009). Rheumatoid Arthritis: National Clinical Guideline for Management and Treatment in Adults. London, Royal College of Physicians.

Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T and Azuma J (2009). Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. Ann Rheum Dis 68: 1580-4.

Nissilä M, Isomäki H, Kaarela K, Kiviniemi P, Martio J and Sarna S (1983). Prognosis of inflammatory joint diseases. A three-year follow-up study. Scand J Rheumatol 12: 33-8.

O'Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ, Garwood V, Maloley P, Klassen LW, Wees S, Klein H and Moore GF (1996). Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 334: 1287-91.

Pinals RS, Masi AT and Larsen RA (1981). Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 24: 1308-15.

Pincus T, Callahan LF, Sale WG, Brooks AL, Payne LE and Vaughn WK (1984). Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. Arthritis Rheum 27: 864-72.

Pincus T, Yazici Y, Sokka T, Aletaha D and Smolen JS (2003). Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. Clin Exp Rheumatol 21: S179-85.

Pincus T and Sokka T (2006). Quantitative measures to assess patients with rheumatic diseases: 2006 update. Rheum Dis Clin North Am 32 Suppl 1: 29-36.

Plosker GL and Croom KF (2005). Sulfasalazine: a review of its use in the management of rheumatoid arthritis. Drugs 65: 1825-49.

Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB and van Riel PL (1995). Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 38: 44-8.

Proudman SM, Keen HI, Stamp LK, Lee AT, Goldblatt F, Ayres OC, Rischmueller M, James MJ, Hill CL, Caughey GE and Cleland LG (2007). Response-driven combination therapy with conventional disease-modifying antirheumatic drugs can achieve high response rates in early rheumatoid arthritis with minimal glucocorticoid and nonsteroidal anti-inflammatory drug use. Semin Arthritis Rheum 37: 99-111.

Puolakka K, Kautiainen H, Möttönen T, Hannonen P, Korpela M, Julkunen H, Luukkainen R, Vuori K, Paimela L, Blåfield H, Hakala M and Leirisalo-Repo M (2004). Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. Arthritis Rheum 50: 55-62.

Puolakka K, Kautiainen H, Möttönen T, Hannonen P, Korpela M, Hakala M, Järvinen P, Ahonen J, Forsberg S and Leirisalo-Repo M (2005a). Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. Arthritis Rheum 52: 36-41.

Puolakka K, Kautiainen H, Möttönen T, Hannonen P, Hakala M, Korpela M, Ilva K, Yli-Kerttula U, Piirainen H and Leirisalo-Repo M (2005b). Predictors of productivity loss in early rheumatoid arthritis: a 5 year follow up study. Ann Rheum Dis 64: 130-3.

Puolakka K, Kautiainen H, Pekurinen M, Möttönen T, Hannonen P, Korpela M, Hakala M, Arkela-Kautiainen M, Luukkainen R and Leirisalo-Repo M (2006). Monetary value of lost productivity over a 5-year follow up in early rheumatoid arthritis estimated on the basis of official register data on patients' sickness absence and gross income: experience from the FIN-RACo Trial. Ann Rheum Dis 65: 899-904.

Puolakka K, Kautiainen H, Pohjolainen T and Virta L (2010). No increased mortality in incident cases of rheumatoid arthritis during the new millennium. Ann Rheum Dis 69: 2057-8.

Rezaei H, Saevarsdottir S, Forslind K, Albertsson K, Wallin H, Bratt J, Ernestam S, Geborek P, Pettersson IF and van Vollenhoven RF (2011). In early rheumatoid arthritis, patients with a good initial response to methotrexate have excellent 2-year clinical outcomes, but radiological progression is not fully prevented: data from the methotrexate responders population in the SWEFOT trial. Ann Rheum Dis.

Ritchie DM, Boyle JA, McInnes JM, Jasani MK, Dalakos TG, Grieveson P and Buchanan WW (1968). Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. Q J Med 37: 393-406.

Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, Paulus HE, Mudano A, Pisu M, Elkins-Melton M, Outman R, Allison JJ, Suarez Almazor M, Bridges SL, Jr., Chatham WW, Hochberg M, MacLean C, Mikuls T, Moreland LW, O'Dell J, Turkiewicz AM and Furst DE (2008). American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 59: 762-84.

Saevarsdottir S, Wedren S, Seddighzadeh M, Bengtsson C, Wesley A, Lindblad S, Askling J, Alfredsson L and Klareskog L (2011). Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. Arthritis Rheum 63: 26-36.

Saraux A, Berthelot JM, Chales G, Le HC, Thorel J, Hoang S, Martin A, Allain J, Nouy-Trolle I, Devauchelle V, Youinou P and Le GP (2002). Second-line drugs used in recent-onset rheumatoid arthritis in Brittany (France). Joint Bone Spine 69: 37-42.

Saunders SA, Capell HA, Stirling A, Vallance R, Kincaid W, McMahon AD and Porter DR (2008). Triple therapy in early active rheumatoid arthritis: a randomized, single-blind, controlled trial comparing step-up and parallel treatment strategies. Arthritis Rheum 58: 1310-7.

Schmajuk G, Schneeweiss S, Katz JN, Weinblatt ME, Setoguchi S, Avorn J, Levin R and Solomon DH (2007). Treatment of older adult patients diagnosed with rheumatoid arthritis: improved but not optimal. Arthritis Rheum 57: 928-34.

Schulze-Koops H, Skapenko A and Cope A (2009). Immunology and the rheumatic diseases. EULAR Compendium on Rheumatic Diseases, BMJ Publishing Group and European League Against Rheumatism**:** 47-60.
Scire CA, Verstappen SM, Mirjafari H, Bunn DK, Lunt M, Montecucco C, Bruce IN and Symmons DP (2011). Reduction of long-term disability in inflammatory polyarthritis by early and persistent suppression of joint inflammation: results from the Norfolk Arthritis Register. Arthritis Care Res (Hoboken) 63: 945-52.

Scott DL and Strand V (2002). The effects of disease-modifying anti-rheumatic drugs on the Health Assessment Questionnaire score. Lessons from the leflunomide clinical trials database. Rheumatology (Oxford) 41: 899-909.

Sharp JT, Wolfe F, Lassere M, Boers M, Van Der Heijde D, Larsen A, Paulus H, Rau R and Strand V (2004). Variability of precision in scoring radiographic abnormalities in rheumatoid arthritis by experienced readers. J Rheumatol 31: 1062-72.

Sievers K, Hurri L and Sievers UM (1963). A Comparative Study of the Effects of Gold Chloroquine and Combined Gold-Chloroquine Therapy in the Treatment of Rheumatoid Arthritis. Reumatologia 1: 203-10.

Sihvonen S, Korpela M, Laippala P, Mustonen J and Pasternack A (2004). Death rates and causes of death in patients with rheumatoid arthritis: a population-based study. Scand J Rheumatol 33: 221-7.

Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Tanjong Ghogomu E and Tugwell P (2009). Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev: CD007848.

Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, Filippini G, Skoetz N, Francis D, Lopes LC, Guyatt GH, Schmitt J, La Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Lunn MP, Tugwell P and Buchbinder R (2011a). Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev: CD008794.

Singh JA, Beg S and Lopez-Olivo MA (2011b). Tocilizumab for rheumatoid arthritis. Cochrane Database Syst Rev: CD008331.

Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, Loew-Friedrich I, Oed C and Rosenburg R (1999). Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group. Lancet 353: 259-66.

Smolen JS, Han C, van der Heijde D, Emery P, Bathon JM, Keystone E, Kalden JR, Schiff M, Bala M, Baker D, Han J, Maini RN and St Clair EW (2006). Infliximab treatment maintains employability in patients with early rheumatoid arthritis. Arthritis Rheum 54: 716-22.

Smolen J, Landewe RB, Mease P, Brzezicki J, Mason D, Luijtens K, van Vollenhoven RF, Kavanaugh A, Schiff M, Burmester GR, Strand V, Vencovsky J and van der Heijde D (2009). Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis 68: 797-804.

Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, Gorter S, Knevel R, Nam J, Schoels M, Aletaha D, Buch M, Gossec L, Huizinga T, Bijlsma JW, Burmester G, Combe B, Cutolo M, Gabay C, Gomez-Reino J, Kouloumas M, Kvien TK, Martin-Mola E, McInnes I, Pavelka K, van Riel P, Scholte M, Scott DL, Sokka T, Valesini G, van Vollenhoven R, Winthrop KL, Wong J, Zink A and van der Heijde D (2010a). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 69: 964-75.

Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, Combe B, Cutolo M, de Wit M, Dougados M, Emery P, Gibofsky A, Gomez-Reino JJ, Haraoui B, Kalden J, Keystone EC, Kvien TK, McInnes I, Martin-Mola E, Montecucco C, Schoels M and van der Heijde D (2010b). Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 69: 631-7.

Sokka T, Kautiainen H, Mottonen T and Hannonen P (1999a). Work disability in rheumatoid arthritis 10 years after the diagnosis. J Rheumatol 26: 1681-5.

Sokka T, Möttönen T and Hannonen P (1999b). Mortality in early "sawtooth" treated rheumatoid arthritis patients during the first 8-14 years. Scand J Rheumatol 28: 282-7.

Sokka T, Möttönen T and Hannonen P (2000). Disease-modifying anti-rheumatic drug use according to the 'sawtooth' treatment strategy improves the functional outcome in rheumatoid arthritis: results of a long-term follow-up study with review of the literature. Rheumatology (Oxford) 39: 34-42.

Sokka T and Pincus T (2002). Contemporary disease modifying antirheumatic drugs (DMARD) in patients with recent onset rheumatoid arthritis in a US private practice: methotrexate as the anchor drug in 90% and new DMARD in 30% of patients. J Rheumatol 29: 2521-4.

Sokka T, Kautiainen H, Hannonen P and Pincus T (2006). Changes in Health Assessment Questionnaire disability scores over five years in patients with rheumatoid arthritis compared with the general population. Arthritis Rheum 54: 3113-8.

Sokka T, Mäkinen H, Hannonen P and Pincus T (2007a). Most people over age 50 in the general population do not meet ACR remission criteria or OMERACT minimal disease activity criteria for rheumatoid arthritis. Rheumatology (Oxford) 46: 1020-3.

Sokka T, Kautiainen H, Toloza S, Mäkinen H, Verstappen SM, Lund Hetland M, Naranjo A, Baecklund E, Herborn G, Rau R, Cazzato M, Gossec L, Skakic V, Gogus F, Sierakowski S, Bresnihan B, Taylor P, McClinton C and Pincus T (2007b). QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Ann Rheum Dis 66: 1491-6.

Sokka T, Envalds M and Pincus T (2008). Treatment of rheumatoid arthritis: a global perspective on the use of antirheumatic drugs. Mod Rheumatol 18: 228-39.

Sokka T and Pincus T (2009). Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35%-45% of patients with rheumatoid arthritis seen between 1980 and 2004: analyses from Finland and the United States. J Rheumatol 36: 1387-90.

Sokka T, Kautiainen H, Pincus T, Verstappen SM, Aggarwal A, Alten R, Andersone D, Badsha H, Baecklund E, Belmonte M, Craig-Muller J, da Mota LM, Dimic A, Fathi NA, Ferraccioli G, Fukuda W, Geher P, Gogus F, Hajjaj-Hassouni N, Hamoud H, Haugeberg G, Henrohn D, Horslev-Petersen K, Ionescu R, Karateew D, Kuuse R, Laurindo IM, Lazovskis J, Luukkainen R, Mofti A, Murphy E, Nakajima A, Oyoo O, Pandya SC, Pohl C, Predeteanu D, Rexhepi M, Rexhepi S, Sharma B, Shono E, Sibilia J, Sierakowski S, Skopouli FN, Stropuviene S, Toloza S, Valter I, Woolf A and Yamanaka H (2010). Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. Arthritis Res Ther 12: R42.

Spies CM, Bijlsma JW, Burmester GR and Buttgereit F (2010). Pharmacology of glucocorticoids in rheumatoid arthritis. Curr Opin Pharmacol 10: 302-7.

St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, Keystone E, Schiff M, Kalden JR, Wang B, Dewoody K, Weiss R and Baker D (2004). Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 50: 3432-43.

Suarez-Almazor ME, Belseck E, Shea B, Wells G and Tugwell P (2000a). Sulfasalazine for rheumatoid arthritis. Cochrane Database Syst Rev: CD000958.

Suarez-Almazor ME, Belseck E, Shea B, Homik J, Wells G and Tugwell P (2000b). Antimalarials for rheumatoid arthritis. Cochrane Database Syst Rev: CD000959.

Symmons DP and Silman AJ (2006). Aspects of early arthritis. What determines the evolution of early undifferentiated arthritis and rheumatoid arthritis? An update from the Norfolk Arthritis Register. Arthritis Res Ther 8: 214.

Syversen SW, Gaarder PI, Goll GL, Odegard S, Haavardsholm EA, Mowinckel P, van der Heijde D, Landewe R and Kvien TK (2008). High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. Ann Rheum Dis 67: 212-7.

Tavares R, Pope JE, Tremblay JL, Thorne C, Bykerk VP, Lazovskis J, Blocka KL, Bell MJ, Lacaille D, Hitchon CA, Fitzgerald AA, Fidler WK, Bookman AA, Henderson JM, Mosher DP, Sholter DE, Khraishi M, Haraoui B, Chen H, Li X, Laupacis A, Boire G, Tomlinson G and Bombardier C (2011). Early Management of Newly Diagnosed Rheumatoid Arthritis by Canadian Rheumatologists: A National, Multicenter, Retrospective Cohort. J Rheumatol.

Taylor P, Gartemann J, Hsieh J and Creeden J (2011). A systematic review of serum biomarkers anti-cyclic citrullinated Peptide and rheumatoid factor as tests for rheumatoid arthritis. Autoimmune Dis 2011: 815038.

Tiippana-Kinnunen T, Laasonen L, Kautiainen H, Paimela L and Leirisalo-Repo M (2011). Impact of early radiographic remission on the 15-year radiographic outcome in patients with rheumatoid arthritis. Scand J Rheumatol 40: 263-8.

Tosh JC, Wailoo AJ, Scott DL and Deighton CM (2011). Cost-effectiveness of combination nonbiologic disease-modifying antirheumatic drug strategies in patients with early rheumatoid arthritis. J Rheumatol 38: 1593-600.

Tugwell P and Boers M (1993). Developing consensus on preliminary core efficacy endpoints for rheumatoid arthritis clinical trials. OMERACT Committee. J Rheumatol 20: 555-6.

van den Hout WB, Goekoop-Ruiterman YP, Allaart CF, de Vries-Bouwstra JK, Hazes JM, Kerstens PJ, van Zeben D, Hulsmans HM, de Jonge-Bok JM, de Sonnaville PB, Dijkmans BA and Breedveld FC (2009). Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. Arthritis Rheum 61: 291-9.

van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, van Rijswijk MH and van de Putte LB (1990). Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 49: 916-20.

van der Heijde D (2000). How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 27: 261-3.

van der Heijde D and Östergard M (2009). Assessment of disease activity and damage in inflammatory arthritis. EULAR Compendium on Rheumatic Diseases, BMJ Publishing Group and European League Against Rheumatism**:** 182-201.

van der Linden MP, le Cessie S, Raza K, van der Woude D, Knevel R, Huizinga TW and van der Helm-van Mil AH (2010). Long-term impact of delay in assessment of patients with early arthritis. Arthritis Rheum 62: 3537-46.

van Dongen H, van Aken J, Lard LR, Visser K, Ronday HK, Hulsmans HM, Speyer I, Westedt ML, Peeters AJ, Allaart CF, Toes RE, Breedveld FC and Huizinga TW (2007). Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 56: 1424-32.

van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB and van Riel PL (1996). Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 39: 34-40.

van Jaarsveld CH, Jacobs JW, Schrijvers AJ, van Albada-Kuipers GA, Hofman DM and Bijlsma JW (1998). Effects of rheumatoid arthritis on employment and social participation during the first years of disease in The Netherlands. Br J Rheumatol 37: 848-53.

van Nies JA, de Jong Z, van der Helm-van Mil AH, Knevel R, Le Cessie S and Huizinga TW (2010). Improved treatment strategies reduce the increased mortality risk in early RA patients. Rheumatology (Oxford) 49: 2210-6.

van Tuyl LH, Plass AM, Lems WF, Voskuyl AE, Dijkmans BA and Boers M (2007). Why are Dutch rheumatologists reluctant to use the COBRA treatment strategy in early rheumatoid arthritis? Ann Rheum Dis 66: 974-6.

van Tuyl LH, Lems WF, Voskuyl AE, Kerstens PJ, Garnero P, Dijkmans BA and Boers M (2008). Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90% remission in a pilot trial. Ann Rheum Dis 67: 1574-7.

van Tuyl LH, Felson DT, Wells G, Smolen J, Zhang B and Boers M (2010a). Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. Arthritis Care Res (Hoboken) 62: 108-17.

van Tuyl LH, Boers M, Lems WF, Landewe RB, Han H, van der Linden S, van de Laar M, Westhovens R, van Denderen JC, Westedt ML, Peeters AJ, Jacobs P, Huizinga TW, van de Brink H, Dijkmans BA and Voskuyl AE (2010b). Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. Ann Rheum Dis 69: 807-12.

van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Coster L, Waltbrand E, Zickert A, Theander J, Thorner A, Hellstrom H, Teleman A, Dackhammar C, Akre F, Forslind K, Ljung L, Oding R, Chatzidionysiou A, Wornert M and Bratt J (2009). Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet 374: 459-66.

Verstappen SM, Bijlsma JW, Verkleij H, Buskens E, Blaauw AA, ter Borg EJ and Jacobs JW (2004). Overview of work disability in rheumatoid arthritis patients as observed in cross-sectional and longitudinal surveys. Arthritis Rheum 51: 488-97.

Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, Blaauw AA and Bijlsma JW (2007). Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 66: 1443-9.

Verstappen SM, Watson KD, Lunt M, McGrother K, Symmons DP and Hyrich KL (2010). Working status in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 49: 1570-7.

Verstappen SM, McCoy MJ, Roberts C, Dale NE, Hassell AB and Symmons DP (2011). Disease activity, smoking, and reproductive-related predictors of poor prognosis in patients with very early inflammatory polyarthritis. J Rheumatol 38: 429-33.

Virjo (2008). Employment rate potential in the Nordic countries: an overview. Copenhagen: Nordic Council of Ministers. TemaNord, 569 [cited 9 June 2008]. Available at: http://www.norden.org/pub/velfaerd/arbetsmarknad/sk/TN2006569.pdf.

Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, Bombardier C, Carmona L, van der Heijde D, Bijlsma JW, Boumpas DT, Canhao H, Edwards CJ, Hamuryudan V, Kvien TK, Leeb BF, Martin-Mola EM, Mielants H, Muller-Ladner U, Murphy G, Ostergaard M, Pereira IA, Ramos-Remus C, Valentini G, Zochling J and Dougados M (2009). Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 68: 1086-93.

Visser K and van der Heijde D (2009). Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis 68: 1094-9.

Ward MM (1999). Trends in the use of disease modifying antirheumatic medications in rheumatoid arthritis, 1980-1995: results from the National Ambulatory Medical Care Surveys. J Rheumatol 26: 546-50.

Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, Jackson CG, Lange M and Burge DJ (1999). A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 340: 253-9.

Wells GA, Boers M, Shea B, Brooks PM, Simon LS, Strand CV, Aletaha D, Anderson JJ, Bombardier C, Dougados M, Emery P, Felson DT, Fransen J, Furst DE, Hazes JM, Johnson KR, Kirwan JR, Landewe RB, Lassere MN, Michaud K, Suarez-Almazor M, Silman AJ, Smolen JS, Van der Heijde DM, van Riel PL, Wolfe F and Tugwell PS (2005). Minimal disease activity for rheumatoid arthritis: a preliminary definition. J Rheumatol 32: 2016-24.

Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA and van Riel PL (2001). The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 44: 2009-17.

Welsing PM, Landewe RB, van Riel PL, Boers M, van Gestel AM, van der Linden S, Swinkels HL and van der Heijde DM (2004). The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 50: 2082-93.

Westlake SL, Colebatch AN, Baird J, Kiely P, Quinn M, Choy E, Ostor AJ and Edwards CJ (2010). The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. Rheumatology (Oxford) 49: 295-307.

WHO Collaborating Centre for Drug Statistics Methodology. Last updated: 2009-03-06 Available on internet: http://www.whocc.no/atcddd/.

Williams HJ, Ward JR, Dahl SL, Clegg DO, Willkens RF, Oglesby T, Weisman MH, Schlegel S, Michaels RM, Luggen ME and et al. (1988). A controlled trial comparing sulfasalazine, gold sodium thiomalate, and placebo in rheumatoid arthritis. Arthritis Rheum 31: 702-13.

Wilske KR and Healey LA (1989). Remodeling the pyramid--a concept whose time has come. J Rheumatol 16: 565-7.

Wolfe F and Hawley DJ (1998). The longterm outcomes of rheumatoid arthritis: Work disability: a prospective 18 year study of 823 patients. J Rheumatol 25: 2108-17.

Wolfe F and Zwillich SH (1998). The long-term outcomes of rheumatoid arthritis: a 23-year prospective, longitudinal study of total joint replacement and its predictors in 1,600 patients with rheumatoid arthritis. Arthritis Rheum 41: 1072-82.

Wolfe F (2001). Which HAQ is best? A comparison of the HAQ, MHAQ and RA-HAQ, a difficult 8 item HAQ (DHAQ), and a rescored 20 item HAQ (HAQ20): analyses in 2,491 rheumatoid arthritis patients following leflunomide initiation. J Rheumatol 28: 982-9.

Wolfe F, Allaire S and Michaud K (2007a). The prevalence and incidence of work disability in rheumatoid arthritis, and the effect of anti-tumor necrosis factor on work disability. J Rheumatol 34: 2211-7.

Wolfe F, Rasker JJ, Boers M, Wells GA and Michaud K (2007b). Minimal disease activity, remission, and the long-term outcomes of rheumatoid arthritis. Arthritis Rheum 57: 935-42.

Woodrick RS and Ruderman EM (2011). Safety of biologic therapy in rheumatoid arthritis. Nat Rev Rheumatol 7: 639-52.

Yamanaka H, Inoue E, Singh G, Tanaka E, Nakajima A, Taniguchi A, Hara M, Tomatsu T and Kamatani N (2007). Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan. Mod Rheumatol 17: 283-9.

Yazici Y, Sokka T and Pincus T (2009). Radiographic measures to assess patients with rheumatoid arthritis: advantages and limitations. Rheum Dis Clin North Am 35: 723-9, vi.

Yelin E (1992). Arthritis. The cumulative impact of a common chronic condition. Arthritis Rheum 35: 489-97.

Yelin E, Trupin L, Katz P, Lubeck D, Rush S and Wanke L (2003). Association between etanercept use and employment outcomes among patients with rheumatoid arthritis. Arthritis Rheum 48: 3046-54.

Young A, Dixey J, Kulinskaya E, Cox N, Davies P, Devlin J, Emery P, Gough A, James D, Prouse P, Williams P and Winfield J (2002). Which patients stop working because of rheumatoid arthritis? Results of five years' follow up in 732 patients from the Early RA Study (ERAS). Ann Rheum Dis 61: 335-40.

Ziegler S, Huscher D, Karberg K, Krause A, Wassenberg S and Zink A (2010). Trends in treatment and outcomes of rheumatoid arthritis in Germany 1997-2007: results from the National Database of the German Collaborative Arthritis Centres. Ann Rheum Dis 69: 1803-8.

Zink A, Listing J, Klindworth C and Zeidler H (2001). The national database of the German Collaborative Arthritis Centres: I. Structure, aims, and patients. Ann Rheum Dis 60: 199-206.

ORIGINAL PUBLICATIONS

I *Arthritis Rheumatism, 60: 1222-31 © 2009*, reprinted with the permission from John Wiley and Sons

II *Arthritis Research and Therapy, 12: R122 © 2010,* reprinted according to the Biomed Central Open Access agreement

III *Scandinavian Journal of Rheumatogy, 40: 16-21 © 2011,* reprinted with the permission from the Informa Healthcare

IV *Annals of the Rheumatic Diseases, in press,* reprinted with the permission from the BMJ Publishing Group

ARTHRITIS & RHEUMATISM
Vol. 60, No. 5, May 2009, pp 1222–1231
DOI 10.1002/art.24447

The Good Initial Response to Therapy With a Combination of Traditional Disease-Modifying Antirheumatic Drugs Is Sustained Over Time

The Eleven-Year Results of the Finnish Rheumatoid Arthritis Combination Therapy Trial

Vappu Rantalaiho,[1] Markku Korpela,[1] Pekka Hannonen,[2] Hannu Kautiainen,[3] Salme Järvenpää,[4] Marjatta Leirisalo-Repo,[5] Markku Hakala,[6] Kari Puolakka,[7] Heikki Julkunen,[8] Riitta Luosujärvi,[5] and Timo Möttönen,[9] for the FIN-RACo Trial Group

Objective. **To evaluate the evolution of functional and clinical outcomes over 11 years in patients with early rheumatoid arthritis (RA) initially treated with a combination of 3 disease-modifying antirheumatic drugs (DMARDs) or with a single DMARD.**

Methods. **A cohort of 199 patients with early active RA were initially randomized to receive treatment with a combination of methotrexate, sulfasalazine, and hydroxychloroquine with prednisolone or treatment with a single DMARD (initially, sulfasalazine) with or without prednisolone. After 2 years, the drug treatment strategy became unrestricted, but still targeted remission. At 11 years, function was assessed with the Health Assessment Questionnaire (HAQ), and clinical outcomes were assessed with the modified Minimal Disease Activity (MDA) measure and the American College of Rheumatology (ACR) criteria for remission.**

Results. **At 11 years, 138 patients were assessed (68 in the combination-DMARD group and 70 in the single-DMARD group). The mean ± SD HAQ scores were 0.34 ± 0.54 in the combination-DMARD group and 0.38 ± 0.58 in the single-DMARD group ($P = 0.88$). Modified MDA was achieved by 63% (95% confidence interval [95% CI] 51, 77) and by 43% (95% CI 32, 55) ($P = 0.016$) of the combination-DMARD group and the single-DMARD group, respectively, and ACR remission by 37% (95% CI 26, 49) and by 19% (95% CI 11, 29) ($P = 0.017$), respectively.**

Conclusion. **Initial therapy with a combination of DMARDs in early RA results in higher rates of patients achieving modified MDA and strict ACR remission even over the long term than initial single-DMARD therapy. Targeting remission with tight clinical controls results in good functional and clinical outcomes in most RA patients.**

Rheumatoid arthritis (RA) influences the patient's quality of life and even the patient's lifespan. During the early years of RA, active inflammation limits functional capacity, and later, progressive joint destruction may cause disability (1). Impaired working capacity causes expenses both for the individual and for the society. Furthermore, rates of premature death are increased in RA patients (2).

Supported by the Medical Research Fund of Tampere University Hospital and by the Finnish Society for Rheumatology.

[1]Vappu Rantalaiho, MD, Markku Korpela, MD, PhD: Tampere University Hospital, Tampere, Finland; [2]Pekka Hannonen, MD, PhD: Jyväskylä Central Hospital, Jyväskylä, Finland; [3]Hannu Kautiainen, BA: Orton Foundation, Helsinki, Finland; [4]Salme Järvenpää, MSc: Medcare Foundation, Äänekoski, Finland; [5]Marjatta Leirisalo-Repo, MD, PhD, Riitta Luosujärvi, MD, PhD: Helsinki University Central Hospital, Helsinki, Finland; [6]Markku Hakala, MD, PhD: Rheumatism Foundation Hospital, Heinola, and University of Tampere, Tampere, Finland; [7]Kari Puolakka, MD, PhD: Lappeenranta Central Hospital, Lappeenranta, Finland; [8]Heikki Julkunen, MD, PhD: Peijas Hospital, Vantaa, Finland; [9]Timo Möttönen, MD, PhD: Turku University Hospital, Turku, Finland.

Dr. Hakala has received consulting fees, speaking fees, and/or honoraria from Abbott, Merck, Sharp, and Dohme, Ratiopharm, Roche, Schering-Plough, and Wyeth (less than $10,000 each).

Address correspondence and reprint requests to Vappu Rantalaiho, MD, Department of Internal Medicine, Centre for Rheumatic Diseases, Tampere University Hospital, PO Box 2000, FI-33521 Tampere, Finland. E-mail: vappu.rantalaiho@pshp.fi.

Submitted for publication May 22, 2008; accepted in revised form January 19, 2009.

Recent evidence shows that early and aggressive treatment with traditional disease-modifying antirheumatic drugs (DMARDs) (3–5) as well as with biologic agents, eliminating the activity of tumor necrosis factor α (6–8), alters the disease course in the short term. Effective early therapy with combinations of conventional DMARDs has also been shown to retard the radiologic progression of joint damage in RA patients and, thus, to reduce the probability of chronic disability (9,10). However, the effects of the more aggressive therapy on the long-term prognosis of RA patients are unknown. Longer followup studies of RA patients receiving different treatment strategies are therefore needed. This issue is emphasized when considering the chronic nature of RA with the potentially high costs of treatment as well as the considerable indirect costs.

We have previously reported that early RA patients treated with a combination of DMARDs more frequently reached clinical remission and had less radiographic progression at 2 years as compared with patients treated with a single DMARD (4). Furthermore, despite the change to an unrestricted treatment strategy after 2 years, less radiologic joint destruction was still present at 5 years (4,10). The good clinical response seen at 6 months in those receiving a combination of conventional DMARDs also translated into better maintenance of working capacity at 5 years (11,12).

The main purpose of the present study was to examine whether the treatment strategy used during the first 2 years had a long-term impact on the outcome of RA as assessed by self-reported function, by clinical disease activity determined by various disease activity measures, as well as by death and other serious adverse events over 11 years.

PATIENTS AND METHODS

Patients. From April 1993 to May 1995, a total of 199 DMARD-naive patients with RA of recent onset (symptom duration <2 years; median 6 months) were admitted to this multicenter, parallel-group, randomized study comparing the efficacy and tolerability of treatment with either a combination of DMARDs (methotrexate, sulfasalazine, and hydroxychloroquine, with prednisolone) or a single DMARD (initially, sulfasalazine, with or without prednisolone) (4).

The patient selection criteria were as follows: fulfillment of the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria for RA (13), age 18–65 years, duration of symptoms <2 years, and active disease, with ≥ 3 swollen joints and at least 3 of the following 4 features: either an erythrocyte sedimentation rate (ESR) ≥ 28 mm/hour or a C-reactive protein level >19 mg/liter, morning stiffness ≥ 29 minutes in duration, >5 swollen joints, and >10 tender joints.

Study design during the first 2 years. Combination-DMARD therapy was started with methotrexate 7.5 mg/week, sulfasalazine 500 mg twice daily, and hydroxychloroquine 300 mg/day, with prednisolone 5 mg/day, but the dosages could be adjusted to achieve remission. The highest dosages allowed were 15 mg/week for methotrexate, 2 gm/day for sulfasalazine, and 10 mg/day for prednisolone. If any of the components of the drug combination had to be discontinued for any reason, a combination of 3 DMARDs was restarted by replacing the discontinued DMARD with a different DMARD, as described in detail previously (4).

Single-DMARD treatment was initiated according to the "sawtooth" strategy (14), using sulfasalazine (2 gm/day) as the initial drug for all patients. The dosage was allowed to be increased to 3 gm/day, and the simultaneous use of prednisolone up to 10 mg/day was allowed. If an adverse event occurred or if the clinical response was insufficient, sulfasalazine was replaced with methotrexate or, after that, with a different single DMARD.

Treatment was targeted toward remission in all patients. Intraarticular injections of glucocorticoids into inflamed joints were allowed, based on the judgment of the attending rheumatologist.

Study design from year 2 to year 5. After 2 years, treatment was still aimed at achieving or maintaining remission, but the choice and use of DMARDs was unrestricted. Thus, regardless of the original randomization group, patients who had an insufficient response could be treated liberally with increased dosages of DMARDs (e.g., methotrexate up to 25 mg/week orally or parenterally, sulfasalazine up to 3 gm/day) and with DMARD combinations when clinically indicated and tolerated. During long-term remission, however, the protocol required drug dosages to be reduced and eventually tapered off. The first drug to be tapered off was prednisolone. If it could be discontinued without losing remission, other DMARDs could be tapered down, 1 DMARD per year, by gradually reducing the dosage. If the RA was reactivated, the last medication and dosage at which remission was maintained was reinstituted (10).

Study design after 5 years. After 5 years, most of the patients were followed up at the original participating centers by the same rheumatologist and were treated according to his or her clinical judgment. The treatment was still targeted toward remission. As a consequence, depending on the clinical situation, the drug therapies of the study patients could vary from no DMARDs or prednisolone to a combination of DMARDs as well as to biologic agents. All patients who had participated in the 5-year followup survey were invited to participate in the 11-year followup visit.

Clinical assessments. All clinical assessments were performed by the treating rheumatologist. Outcome measures included the patient's self report of physical functioning and assessment of RA clinical activity, as well as the indices of disease activity required to determine the frequency of remissions. The medications used by the patients were recorded at each study visit. DMARD strategies used between year 2 and year 11 were carefully elucidated based on the patient's self report and his or her medical records. Serious adverse events, including death, malignant disorders, any life-threatening

event, and any event that necessitated hospital admission, among the patients participating in the 11-year followup were recorded. The vital status of all patients in whom the study medication was initiated was determined by inquiry from the Local Register Office. Death certificates for all deceased patients were obtained from the office of Statistics Finland.

Functional capacity was assessed with the Health Assessment Questionnaire (HAQ) (15). Clinical activity of RA was assessed with the Disease Activity Score 28-joint assessment (DAS28) (16), which was calculated with the following formula:

$$\text{DAS28} = 0.56 \times \sqrt{(\text{TJC28})} + 0.28 \times \sqrt{(\text{SJC28})} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH}$$

where TJC28 represents the tender joint count in 28 joints, SJC28 represents the swollen joint count in 28 joints, and GH represents general health.

Criteria for the modified Minimal Disease Activity (MDA) (17) were no swollen joints, no tender joints, and an ESR ≤10 mm/hour or fulfillment of at least 5 of the following 7 criteria: swollen joint count ≤1 (range 0–52), tender joint count ≤1 (range 0–52), HAQ score ≤0.5 (range 0–3), visual analog scale (0–100-mm scale) score for pain ≤20, for the patient's global assessment of disease activity ≤20, and for the physician's global assessment of disease activity ≤15, and an ESR ≤20 mm/hour. Use of a 52-joint count of tender and swollen joints instead of the 28-joint count used in the original analysis (17) made our modified criteria more stringent.

Remission was defined as fulfillment of 5 of the ACR criteria (18), excluding fatigue and duration of remission. Thus, a patient whose RA was designated as being in remission could not have any tender or painful joints, no swollen joints or tendon sheaths, no elevation of the ESR (normal <30 mm/hour in women and <20 mm/hour in men), and a duration of morning stiffness of ≤15 minutes. Remission according to the DAS28 was defined as score of <2.6 (19).

Ethical considerations. The study was performed according to the principles of the Declaration of Helsinki. The protocol was approved by the national health authorities and ethics committees of all 18 participating hospitals. All patients gave written informed consent.

Statistical analysis. Results are presented as the mean ± SD, the median with the interquartile range (IQR), or counts with percentages. The 95% confidence intervals (95% CIs) are given for the most important outcomes. Statistical comparison between groups was performed with the *t*-test, permutation test, chi-square test, or Fisher's exact test, as appropriate. Repeated measures for continuous and binary outcomes were analyzed using generalized estimating equation (GEE) models with the exchangeable correlation structure. GEE models do not require complete data and can be fit even when individuals do not have observations at all time points. The Cox proportional hazards model was used to estimate age- and sex-adjusted risk of death between groups. The standardized mortality ratio (i.e., the ratio of observed to expected deaths) was calculated using the subject-years method with 95% CIs, assuming a Poisson distribution. Probabilities of survival in an age- and sex-matched sample of the general population between 1993 and 2006 were calculated from data from the Official Statistics of Finland.

RESULTS

A flow chart of the study patients is shown in Figure 1. Of the 199 patients originally randomized to the study, 195 started treatment, 97 in the combination-DMARD therapy group and 98 in the single-DMARD therapy group (starting with sulfasalazine). In each

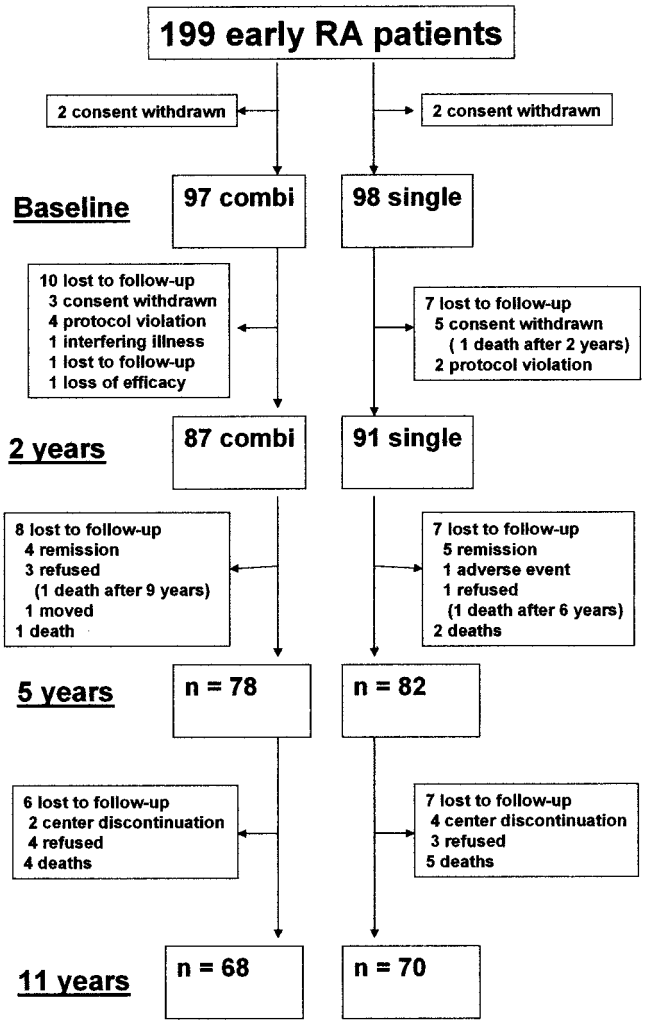

Figure 1. Flow chart showing the distribution of the rheumatoid arthritis study patients from initial screening to the 11-year followup visit. Patients were randomized at baseline to receive a combination (combi) of 3 disease-modifying antirheumatic drugs (DMARDs), consisting of methotrexate, sulfasalazine, and hydroxychloroquine, with prednisolone, or to receive a single DMARD, consisting of sulfasalazine, with or without prednisolone. After year 2 of study, the choice of DMARDs was unrestricted (see Patients and Methods for details).

Table 1. Demographic features at baseline and clinical characteristics at baseline and at 11 years in the 138 RA patients who participated in the 11-year followup visit, by initial randomization group*

Characteristic	Randomization group for the first 2 years	
	Combination-DMARD group (n = 68)	Single-DMARD group (n = 70)
Demographics at baseline		
Female, no. (%)	42 (62)	48 (69)
Age, mean ± SD years	46 ± 9	47 ± 11
Duration of RA, median (IQR) months	6 (4–9)	7 (4–12)
Rheumatoid factor, no. (%)	49 (72)	46 (66)
Measures of disease activity at baseline		
DAS28, mean ± SD	5.39 ± 0.86	5.65 ± 1.13
Erythrocyte sedimentation rate, median (IQR) mm/hour	27 (16–48)	33 (22–54)
No. of swollen joints, median (IQR)	13 (9–16)	13 (10–16)
No. of tender joints, median (IQR)	16 (12–22)	16 (13–24)
Patient's global assessment of disease activity, by VAS, median (IQR) mm	48 (29–65)	47 (30–61)
Pain, by VAS, median (IQR) mm	47 (27–63)	48 (26–61)
Physician's global assessment of disease activity, by VAS, median (IQR) mm	38 (31–54)	43 (30–59)
Physical function, by HAQ, mean ± SD score	0.82 ± 0.53	0.90 ± 0.63
Measures of disease activity at 11 years		
DAS28, mean ± SD	2.48 ± 1.22	2.73 ± 1.23
Erythrocyte sedimentation rate, median (IQR) mm/hour	10 (6–21)	13 (6–20)
No. of swollen joints, median (IQR)	0 (0–3)	2 (0–4)
No. of tender joints, median (IQR)	1 (0–5)	2 (0–5)
Patient's global assessment of disease activity, by VAS, median (IQR) mm	16 (3–35)	19 (5–36)
Pain, by VAS, median (IQR) mm	15 (3–30)	16 (5–34)
Physician's global assessment of disease activity, by VAS, median (IQR) mm	5 (1–14)	12 (3–19)†
Physical function, by HAQ, mean ± SD score	0.34 ± 0.54	0.38 ± 0.58

* After the first 2 years of study, the choice of disease-modifying antirheumatic drugs (DMARDs) was unrestricted (see Patients and Methods for details). RA = rheumatoid arthritis; IQR = interquartile range; DAS28 = Disease Activity Score 28-joint assessment; VAS = visual analog scale (range 0–100 mm); HAQ = Health Assessment Questionnaire (range 0–3).
† $P = 0.016$ versus the combination-DMARD group.

group, 2 patients withdrew consent before receiving the first dosage of study medication. The 2-year followup was completed by 178 patients (4) and the 5-year followup by 160 patients (10). Between years 5 and 11, 6 patients in the combination therapy group and 7 in the single therapy group had changed residence, were reluctant to continue the followup, or had been enrolled at a center that did not participate in the study after 5 years (Figure 1). During the entire 11-year followup period, a total of 6 patients in the combination therapy group and 9 in the single therapy group had died.

Thus, a total of 138 patients were assessed at the 11-year visit, 68 in the combination therapy group and 70 in the single therapy group. The baseline demographic and clinical characteristics of the patients were comparable (Table 1). These data were comparable at baseline and at 2 years both between the participants and the dropouts in both study arms. Likewise, the data were comparable between the dropouts of both study groups (data not shown). At 2, 5, and 11 years, data for the measured parameters were available in 96–100% of the patients.

Self-reported physical functioning. The changes in mean HAQ scores in the single and combination therapy groups during the followup period are shown in Figure 2A. The decrease in HAQ scores from baseline to 2 years was statistically significant in both groups ($P < 0.001$), with a decrease of –0.56 (95% CI –0.70, –0.42) in the combination therapy group and –0.61 (95% CI –0.74, –0.47) in the single therapy group. The age-, sex-, and baseline DAS28–adjusted treatment effect over time was not significant ($P = 0.90$). At 11 years, 56% of the combination therapy group and 43% of the single therapy group had a HAQ score of 0. On the other hand, HAQ scores >1 were present in 10% and 9% of the groups, respectively. The distributions of the HAQ scores at the 11-year visit are shown in Figure 2B.

Disease activity according to the modified MDA and the DAS28 and frequency of remissions according to the DAS28 and the ACR criteria. The clinical characteristics of the patients at the 11-year followup visit are shown in Table 1. Clinical disease activity was low in both treatment groups. The only statistically significant difference between the groups was in the physician's

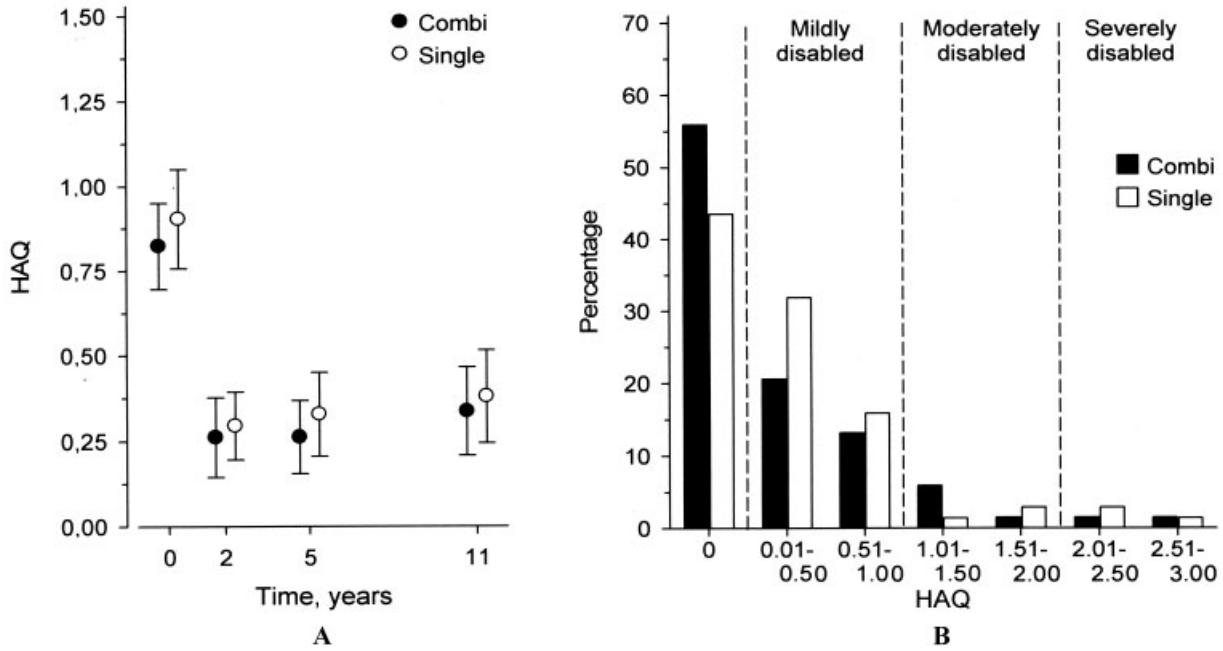

Figure 2. Health Assessment Questionnaire (HAQ) scores in the rheumatoid arthritis study patients. **A,** HAQ scores at baseline and at 2, 5, and 11 years in patients randomized to receive a combination (Combi) of disease-modifying antirheumatic drugs (DMARDs) or a single DMARD. HAQ scores were adjusted for age, sex, and baseline Disease Activity Score 28-joint assessment. Values are the mean and 95% confidence interval. **B,** Distribution of HAQ scores at the 11-year followup visit. Values are the percentages of patients without disability (HAQ score 0) and the percentages with mild, moderate, or severe disability.

global assessment of disease activity, which favored the combination therapy group. However, the modified MDA criteria were met by 63% (95% CI 51, 77) of the patients in the original combination therapy group and by 43% (95% CI 32, 55) of those in the original single therapy group at 11 years ($P = 0.016$).

The mean DAS28 scores are shown in Figure 3A. The treatment effect over time was a significant advantage in the original combination therapy group ($P = 0.0022$). At 2, 5, and 11 years, the mean DAS28 score in patients randomized to combination-DMARD therapy was below the reported DAS28 remission limit (<2.6), while in those randomized to single-DMARD therapy, DAS28 scores remained in the area of low disease activity. DAS28 remission at 11 years was reached by 57% (95% CI 45, 69) of the combination therapy group and by 49% (95% CI 37, 60) of the single therapy group ($P = 0.30$).

Moreover, the strict ACR remission criteria were met by 37% (95% CI 26, 49) of the combination therapy group and by 19% (95% CI 11, 29) of the single therapy group ($P = 0.017$) at 11 years (Figure 3B). The age-, sex-, and baseline DAS28–adjusted treatment effect over time was also significant ($P = 0.0015$). With regard to the ACR remission rates at 2, 5, and 11 years, 13% of the patients in the combination therapy group were in remission at all 3 time points, 54% at 1–2 time points, and 32% at no time points. In the single therapy group, these percentages were 3%, 37%, and 60%, respectively. The difference between the groups was significant ($P = 0.006$, adjusted for age, sex, and baseline DAS28).

Drug treatment and serious adverse events. At 11 years, methotrexate was the most commonly used DMARD, followed by hydroxychloroquine and sulfasalazine. The DMARDs in use at the 11-year visit are shown in Table 2. At the 11-year visit, 32 (47%) of the combination therapy group and 32 (46%) of the single therapy group were taking various combinations of traditional DMARDs. A single DMARD was taken by 15 (22%) and 23 (33%) of the patients in the original combination therapy and single therapy groups, respectively, and no DMARDs by 13 (19%) and 10 (14%) patients, respectively. A biologic agent was taken by 8 (12%) of the patients in the original combination therapy group; in 3 patients, this was taken with a combination of DMARDs and in 5 with a single DMARD. In the original single therapy group, 5 (7%) of the patients were taking a biologic agent; in 2 patients, this was taken with a combination of DMARDs and in 3 with a single DMARD.

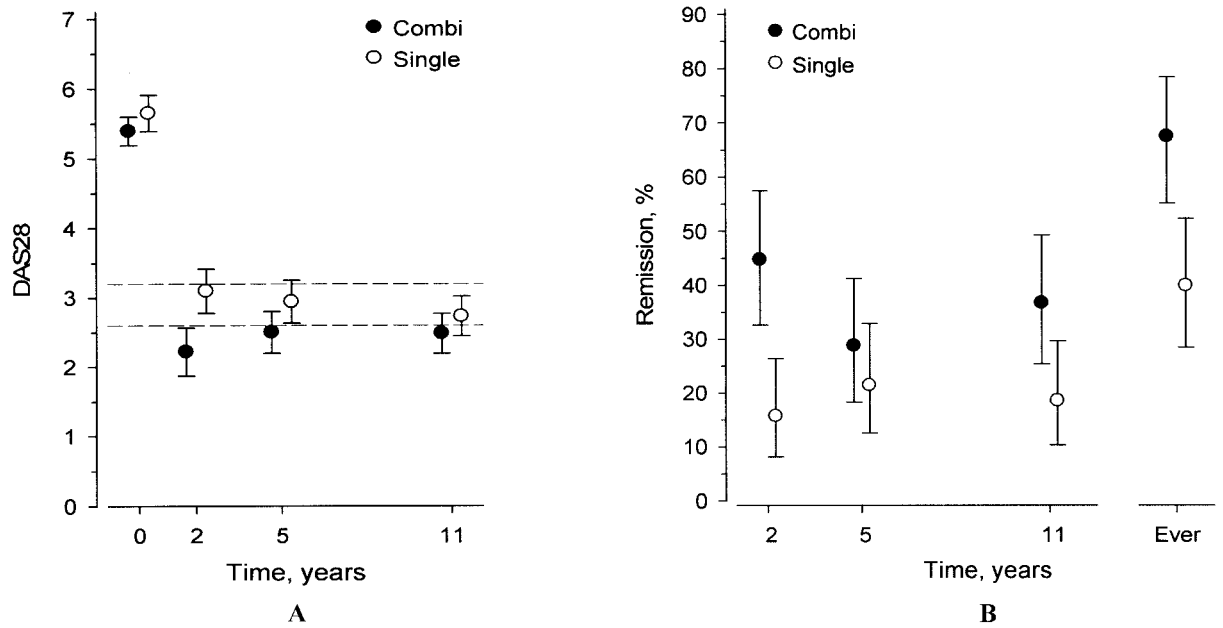

Figure 3. Scores on the Disease Activity Score 28-joint assessment (DAS28) and percentages of patients whose rheumatoid arthritis (RA) was in remission according to the American College of Rheumatology (ACR) criteria. **A,** DAS28 scores at baseline and at 2, 5, and 11 years in patients randomized to receive a combination (Combi) of disease-modifying antirheumatic drugs (DMARDs) or a single DMARD. Values are the mean and 95% confidence interval. Values under the lower broken line (score of 2.6) represent DAS28 remission; values under the upper broken line (score of 3.2) represent low disease activity. **B,** Proportions of patients randomized to receive combination therapy or single therapy whose RA was in strict remission according to the ACR criteria at 2, 5, and 11 years, as well as the proportion of patients whose RA was in strict remission at any of these visits. Values are the mean and 95% confidence interval.

At some time between the 2-year and the 11-year visits, a combination-DMARD strategy had been used by 62 (91%) of the patients in the original combination therapy group and by 56 (80%) of the patients in the original single therapy group ($P = 0.062$). The respective figures for single-DMARD strategy were 39 (57%) of those in the original combination therapy group and 56 (80%) of those in the original single therapy group. Twenty-two (32%) of the patients in the combination group and 27 (39%) of those in the single group had been able to discontinue all DMARDs, at least temporarily, during the followup period from year 2 to year 11. The median percentage of time receiving the combination-DMARD strategy between year 2 and year 11 was 79% (IQR 43–100) in the original combination therapy group and 54% (IQR 3–94) in the original single therapy group ($P = 0.0043$). The respective median percentages for receiving the single-DMARD strategy were 5% (IQR 0–30) and 35% (IQR 3–67) ($P < 0.001$), and the respective median percentages for receiving the no-DMARD strategy were 0% (IQR 0–6) and 0% (IQR 0–8) (P not significant).

The more frequent use of the combination-DMARD strategy between 2 and 11 years in the original combination therapy group, however, had no impact on the frequency of those who met the modified MDA criteria at 11 years. Patients in the original combination

Table 2. Medications in the 138 rheumatoid arthritis patients who participated in the 11-year followup visit, by initial randomization group*

Medications at the 11-year visit	Randomization group for the first 2 years	
	Combination-DMARD group (n = 68)	Single-DMARD group (n = 70)
Methotrexate	39 (57)	42 (60)
Hydroxychloroquine	36 (53)	26 (37)
Sulfasalazine	29 (43)	23 (33)
Leflunomide	2 (3)	7 (10)
Aurothiomalate	2 (3)	4 (6)
Cyclosporine	1 (2)	5 (7)
Auranofin	1 (2)	2 (3)
Podophyllotoxin (CPH 82)	1 (2)	2 (3)
Azathioprine	0 (0)	1 (1)
TNF inhibitors	8 (12)	4 (6)
Rituximab	0 (0)	1 (1)
Prednisolone	22 (32)	33 (47)

* After the first 2 years of study, the choice of disease-modifying antirheumatic drugs (DMARDs) was unrestricted (see Patients and Methods for details). TNF = tumor necrosis factor.

therapy group who met the modified MDA criteria at 11 years and those who did not had received the combination-DMARD strategy (after 2 years) for a median of 54 months (95% CI 46, 62) and 108 months (95% CI 101, 115), respectively ($P < 0.001$). For patients in the original single therapy group, the median times were 51 months (95% CI 11, 91) and 61 months (95% CI 26, 96) ($P = 0.71$), respectively.

The number of serious adverse events between year 5 and year 11 did not differ between the patients in the original combination therapy group and those in the original single therapy group. There were 3 serious infections in the combination therapy group and 4 in the single therapy group. Cardiovascular events occurred in 9 and 7 patients, respectively, and other serious adverse events occurred in 3 and 5 patients, respectively. The number of all malignancies during the 11 years was similar in the 2 study groups, with 6 in the original combination therapy group and 4 in the original single therapy group.

Mortality rates. During the 11-year followup period, a total of 6 patients in the original combination therapy group (6.2% [95% CI 2.8, 13.3]) died: 2 of acute myocardial infarction, 1 of acute arrhythmia (sudden death), 1 of dissection of the ascending aorta, 1 of pneumonia and exacerbation of chronic bronchitis and emphysema, and 1 of malignancy of the lungs. During the same time period, a total of 9 patients in the original single therapy group (9.2% [95% CI 4.9, 16.9]) died: 1 of acute myocardial infarction, 1 of rupture of an abdominal aortic aneurysm, 1 of subarachnoid and intracerebral hemorrhage, 2 of malignancy of the colon, 1 of acute myeloid leukemia, and 3 died in accidents. The age- and sex-adjusted hazard ratio was 1.54 (95% CI 0.54, 4.39) ($P = 0.42$) between groups. The age- and sex-standardized mortality ratio in the entire study group was 1.13 (95% CI 0.64, 1.87).

DISCUSSION

The present followup study shows that in patients with clinically active early RA, initial therapy with a combination of traditional DMARDs as compared with a single DMARD translates into improved long-term outcomes in terms of clinical disease activity and remissions. Furthermore, tight clinical control with adjustments in the active DMARDs and injections of intraarticular corticosteroids preserves function in most of these patients irrespective of the initial DMARD strategy.

The ideal therapy for RA would cure or induce permanent remission of the disease. Currently, the treatment of RA should reduce acute symptoms effectively and safely, have positive effects on the long-term prognosis, and be affordable. There are few truly long-term ($\geq$10 years) followup studies on early RA that include clinical outcomes. Most of these studies have neither a definite nor an active treatment protocol, and the results can be considered to represent the course of conservatively treated RA (20–24).

The management of RA should consist of more than choosing between various DMARDs. It should be targeted toward remission (as in the treatment of malignancies) and should be guided by tight control (as in the treatment of diabetes mellitus). In the present study, we compared the effects of 2 different initial treatment strategies, both of which were targeted toward remission at all time points. The same rheumatologists provided followup care over the course of the study, made predetermined treatment adjustments, and gave intraarticular glucocorticoid injections whenever needed. This treatment policy likely resulted in the observed excellent outcome in the HAQ scores of most of the patients in both study groups.

Other studies of early RA with long-term followup but with more conservative treatment strategies have shown a constantly deteriorating course of the HAQ scores (22,24). However, studies with shorter followup periods and active strategies using a single DMARD (25), combinations of conventional DMARDs (3,9), or biologic agents (6,7) have actually shown functional improvement. In addition, cross-sectional studies comparing earlier and more recent cohorts of RA patients have found a tendency toward better function during the present era, when active DMARD treatment is prevalent (26,27). In our study, the HAQ score decreased after the initiation of DMARD treatment and remained low throughout the entire followup period in both study groups. We emphasize that after 11 years of RA, half of our patients had no disability according to the HAQ score, a finding that is in notable contrast with previously described cohorts (22,24).

After 11 years of RA, the parameters reflecting clinical disease activity also remained low in most of the patients in both study groups. The differences between the patients in the single-DMARD group and those in the combination-DMARD group were small when each parameter was examined separately. Taken together, however, more patients in the combination therapy group than in the single therapy group achieved the modified MDA criteria. For our modification of the MDA criteria, we used a method that applied a 52-joint

count instead of the 28-joint count used in the original analysis (17), which makes our criteria even more stringent than the original MDA criteria. The proportions of patients who achieved remission according to the DAS28 criteria were also rather high in both study groups, although patients in the combination therapy group had more favorable DAS28 scores over time than did those in the single therapy group.

Our requirement for strict adherence to the ACR remission criteria allowed for practically no signs of disease (28). A substantial proportion of the patients in both study groups reached this rigorous target at some point in the study. However, in contrast to the 5-year results, the proportion of patients whose RA was in remission at 11 years was significantly higher in the combination therapy group than in the single therapy group. The sustainability of remission was more frequent in the combination therapy group, whereas never having achieved remission according to the ACR criteria was more characteristic of the single therapy group. Nevertheless, fluctuations between remission and no remission were rather common in both treatment groups. The most plausible explanation for this fluctuation is the fact that a substantial number of patients were near the limit of remission most of the time and, by chance, either above or below the remission limit at the study visits, as shown by DAS28 values as well as the individual parameters reflecting disease activity. However, the odds of being in remission at the followup visits were in favor of the combination treatment group.

The use of DMARDs between year 2 and year 11 differed between groups, with combination treatments used more often in the original combination therapy group. This difference is due, on the one hand, to the protocol, which allowed the tapering of only 1 DMARD per year in a combination group patient whose RA was in remission. On the other hand, the investigators may not have intensified the medications in a noncompliant single-DMARD group patient who was "doing fine," but whose RA was not in remission. However, this had no impact on the clinical outcome at 11 years. In fact, in the combination therapy group, the patients who had met the modified MDA criteria at 11 years had received significantly less combination treatments between 2 years and 11 years than the patients who did not meet the modified MDA criteria at 11 years. In the single-DMARD group, the treatment strategy between 2 and 11 years had no impact on the number of patients who met the modified MDA criteria at 11 years. At the end of the followup, comparable antirheumatic drugs were used irrespective of the initial group allocation. Hence, the most plausible explanation for the higher remission rate during years 2–11 in the combination therapy group is the more intensive initial drug treatment and not the current medication.

This study illuminates the long-term outcome of early RA when starting the initial single-DMARD treatment with sulfasalazine. It can be hypothesized that different results would have been achieved in the single-DMARD group had the first DMARD been methotrexate. In 1993, when this study was begun, the clinical use of methotrexate in RA was far rarer than today, and there were no studies showing its superiority compared with other DMARDs. Even a recent review (29) found no evidence of the superiority of methotrexate in comparison with other DMARDs in terms of clinical efficacy. In our study, the single-DMARD strategy was not tied to sulfasalazine but to a strategy of using 1 DMARD at a time. During the first 2 years, 52% of patients in the single-DMARD group were switched to methotrexate, and some of these patients were further switched to another DMARD (4).

Thus, it seems to us that the superiority of the initial combination treatment may be explained by its sustainability. In the combination therapy group, even if 1 DMARD had to be stopped because of side effects, the patient still had at least 1 other DMARD working. This strategy guaranteed continuing treatment during the therapeutic window of opportunity in early RA.

The present study indicates that even long-term therapy with combinations of conventional DMARDs is safe. No unexpected adverse effects were found in either group after 2 (4), 5 (10), or 11 years of treatment. Also, the observed mortality rate was equal to that in the general population. This finding is consistent with those of some previous studies (30,31).

Our results highlight the concept of a window of opportunity for treatment in RA (32). The short-term advantages of early, tight control of RA have been demonstrated by Scottish (33) and Danish (34,35) studies. The present study shows that the consequences of effective initial treatment extend from sustained low levels of disease activity and preserved functional capacity to normal life expectancy.

The FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy) trial is the first published controlled study of a treatment strategy for RA in which remission was the primary target. Furthermore, the definition of remission we applied allowed for no signs of disease activity. More recently, probably due to the increased options of biologic agents in the treatment of RA, remission as the treatment goal has been widely

accepted. Early strict remission predicts preserved working capacity (12), but the value of more liberal remission levels and the value of strict remission during late disease remain to be proven.

In summary, the natural course of RA can be altered with active DMARD treatment. When the therapy is targeted toward remission and the disease is kept under tight control, which means adjustments to active treatment and intraarticular injections of glucocorticoids when needed, even by starting drug therapy with a single DMARD, the prognosis is better than that in patients described in previous cohorts. However, it is difficult to see why rheumatologists and RA patients should settle for single-DMARD therapy, when by starting with a combination of DMARDs, superior results are achieved without an increase in the number of adverse events. The combination of methotrexate, sulfasalazine, and hydroxychloroquine along with low-dose prednisolone, however, is not the ultimate, perfect treatment of early RA, since it does not cure the disease or produce sustained remission in all patients. Still, in real life, this combination is satisfactory for most patients and, even more importantly, is economically available for a large number of patients worldwide (36). The ideal treatment strategy for the patients in whom this protocol fails remains to be determined by other studies.

AUTHOR CONTRIBUTIONS

Drs. Rantalaiho and Möttönen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Rantalaiho, Korpela, Hannonen, Kautiainen, Leirisalo-Repo, Julkunen, Luosujärvi, Möttönen.

Acquisition of data. Rantalaiho, Korpela, Hannonen, Leirisalo-Repo, Hakala, Puolakka, Julkunen, Luosujärvi, Möttönen.

Analysis and interpretation of data. Rantalaiho, Korpela, Leirisalo-Repo, Möttönen.

Manuscript preparation. Rantalaiho, Korpela, Hannonen, Kautiainen, Järvenpää, Leirisalo-Repo, Hakala, Puolakka, Luosujärvi, Möttönen.

Statistical analysis. Kautiainen, Järvenpää,

REFERENCES

1. Kirwan JR. Links between radiological change, disability, and pathology in rheumatoid arthritis. J Rheumatol 2001;28:881–6.
2. Young A, Koduri G, Batley M, Kulinskaya E, Gough A, Norton S, et al. Mortality in rheumatoid arthritis: increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology (Oxford) 2007;46:350–7.
3. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309–18.
4. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M, et al, for the FIN-RACo Trial Group. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. Lancet 1999;353: 1568–73.
5. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381–90.
6. St.Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al, for the Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50:3432–43.
7. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al, for the PREMIER Investigators. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26–37.
8. Van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al, for the TEMPO Study Investigators. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006;54:1063–74.
9. Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347–56.
10. Korpela M, Laasonen L, Hannonen P, Kautiainen H, Leirisalo-Repo M, Hakala M, et al, for the FIN-RACo Trial Group. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. Arthritis Rheum 2004;50:2072–81.
11. Puolakka K, Kautiainen H, Mottonen T, Hannonen P, Korpela M, Julkunen H, et al, for the FIN-RACo Trial Group. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. Arthritis Rheum 2004;50:55–62.
12. Puolakka K, Kautiainen H, Mottonen T, Hannonen P, Korpela M, Hakala M, et al, for the FIN-RACo Trial Group. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. Arthritis Rheum 2005; 52:36–41.
13. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
14. Fries JF. Reevaluating the therapeutic approach to rheumatoid arthritis: the "sawtooth" strategy. J Rheumatol Suppl 1990;22: 12–5.
15. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
16. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
17. Wells GA, Boers M, Shea B, Brooks PM, Simon LS, Strand CV, et al. Minimal disease activity for rheumatoid arthritis: a preliminary definition. J Rheumatol 2005;32:2016–24.

18. Pinals RS, Masi AT, Larsen RA, and the Subcommittee for Criteria of Remission in Rheumatoid Arthritis of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24:1308–15.
19. Van Riel PL, van Gestel AM. Clinical outcome measures in rheumatoid arthritis. Ann Rheum Dis 2000;59 Suppl 1:i28–31.
20. Jacoby RK, Jayson MI, Cosh JA. Onset, early stages, and prognosis of rheumatoid arthritis: a clinical study of 100 patients with 11-year followup. Br Med J 1973;2:96–100.
21. Corbett M, Dalton S, Young A, Silman A, Shipley M. Factors predicting death, survival and functional outcome in a prospective study of early rheumatoid disease over fifteen years. Br J Rheumatol 1993;32:717–23.
22. Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC, Hazes JM. Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. Arthritis Rheum 1999; 42:1854–60.
23. Jantti JK, Kaarela K, Belt EA, Kautiainen HJ. Incidence of severe outcome in rheumatoid arthritis during 20 years. J Rheumatol 2002;29:688–92.
24. Lindqvist E, Saxne T, Geborek P, Eberhardt K. Ten year outcome in a cohort of patients with early rheumatoid arthritis: health status, disease process, and damage. Ann Rheum Dis 2002;61: 1055–9.
25. Scott DL, Strand V. The effects of disease-modifying antirheumatic drugs on the Health Assessment Questionnaire score: lessons from the leflunomide clinical trials database. Rheumatology (Oxford) 2002;41:899–909.
26. Sokka T, Mottonen T, Hannonen P. Disease-modifying antirheumatic drug use according to the 'sawtooth' treatment strategy improves the functional outcome in rheumatoid arthritis: results of a long-term followup study with review of the literature. Rheumatology (Oxford) 2000;39:34–42.
27. Krishnan E, Fries JF. Reduction in long-term functional disability in rheumatoid arthritis from 1977 to 1998: a longitudinal study of 3035 patients. Am J Med 2003;115:371–6.
28. Makinen H, Kautiainen H, Hannonen P, Sokka T. Frequency of remissions in early rheumatoid arthritis defined by 3 sets of criteria: a 5-year followup study. J Rheumatol 2005;32:796–800.
29. Donahue KE, Gartlehner G, Jonas DE, Lux LJ, Thieda P, Jonas BL, et al. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. Ann Intern Med 2008;148:124–34.
30. Sokka T, Mottonen T, Hannonen P. Mortality in early "sawtooth" treated rheumatoid arthritis patients during the first 8-14 years. Scand J Rheumatol 1999;28:282–7.
31. Kroot EJ, van Leeuwen MA, van Rijswijk MH, Prevoo ML, van 't Hof MA, van de Putte LB, et al. No increased mortality in patients with rheumatoid arthritis: up to 10 years of followup from disease onset. Ann Rheum Dis 2000;59:954–8.
32. Cush JJ. Early rheumatoid arthritis—is there a window of opportunity? J Rheumatol Suppl 2007;80:1–7.
33. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263–9.
34. Hetland ML, Stengaard-Pedersen K, Junker P, Lottenburger T, Ellingsen T, Andersen LS, et al, and the CIMESTRA Study Group. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis Rheum 2006;54:1401–9.
35. Hetland ML, Stengaard-Pedersen K, Junker P, Lottenburger T, Hansen I, Andersen LS, et al. Aggressive combination therapy with intra-articular glucocorticoid injections and conventional disease-modifying antirheumatic-drugs in early rheumatoid arthritis: second year clinical and radiographic results from the CIMESTRA study. Ann Rheum Dis 2008;67:815–22.
36. Sokka T, Hakkinen A, Kautiainen H, Maillefert JF, Toloza S, Mork Hansen T, et al, on behalf of the QUEST-RA Group. Physical inactivity in patients with rheumatoid arthritis: data from twenty-one countries in a cross-sectional, international study. Arthritis Rheum 2008;59:42–50.

APPENDIX A: MEMBERS OF THE FIN-RACo TRIAL GROUP

In addition to the authors, other members of the FIN-RACo Trial Group who contributed to this study during the 11 years are as follows: Jari Ahonen, MD, Harri Blåfield, MD, Kari Eklund, MD, PhD, Sinikka Forsberg, MD, Mikko Hakola, MD Tapani Helve, MD, PhD, Kirsti Ilva, MD, Oili Kaipiainen-Seppänen, MD, PhD, Anna Karjalainen, MD, PhD, Markku Kauppi, MD, PhD, Reijo Luukkainen, MD, PhD, Ilppo Pälvimäki, MD, Ritva Peltomaa, MD, PhD, Tea Uusitalo, MD, Kaisa Vuori, MD, Urpo Yli-Kerttula, MD, PhD. The administrative board responsible for the study consisted of Timo Möttönen, MD, PhD, Markku Hakala, MD, PhD, Pekka Hannonen, MD, PhD, Marjatta Leirisalo-Repo, MD, PhD, and Markku Korpela, MD, PhD.

arthritis research&therapy

RESEARCH ARTICLE Open Access

Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial

Vappu Rantalaiho*[1], Markku Korpela[1], Leena Laasonen[2], Hannu Kautiainen[3,5], Salme Järvenpää[4], Pekka Hannonen[5], Marjatta Leirisalo-Repo[6], Harri Blåfield[7], Kari Puolakka[8], Anna Karjalainen[9], Timo Möttönen[10] for the FIN-RACo Trial Group

Abstract

Introduction: Early treatment of rheumatoid arthritis (RA) has been shown to retard the development of joint damage for a period of up to 5 years. The aim of this study was to evaluate the radiologic progression beyond that time in patients with early RA initially treated with a combination of three disease-modifying antirheumatic drugs (DMARDs) or a single DMARD.

Methods: A cohort of 199 patients with early active RA were initially randomized to receive treatment with a combination of methotrexate, sulfasalazine, and hydroxychloroquine with prednisolone (FIN-RACo), or treatment with a single DMARD (initially, sulfasalazine) with or without prednisolone (SINGLE). After 2 years, the drug-treatment strategy became unrestricted, but still targeted remission. The radiographs of hands and feet were analyzed by using the Larsen score at baseline, 2, 5, and 11 years, and the radiographs of large joints, at 11 years.

Results: Sixty-five patients in the FIN-RACo and 65 in the SINGLE group had radiographs of hands and feet available at baseline and at 11 years. The mean change from baseline to 11 years in Larsen score was 17 (95% CI, 12 to 26) in the FIN-RACo group and 27 (95% CI, 22 to 33) in the SINGLE group ($P = 0.037$). In total, 87% (95% CI, 74 to 94) and 72% (95% CI, 58 to 84) of the patients in the FIN-RACo and the SINGLE treatment arms, respectively, had no erosive changes in large joints at 11 years.

Conclusions: Targeting to remission with tight clinical controls results in low radiologic progression in most RA patients. Patients treated initially with a combination of DMARDs have less long-term radiologic damage than do those treated initially with DMARD monotherapy.

Trial registration : Current Controlled Trials ISRCTN18445519.

Introduction

Conservatively treated cohorts of rheumatoid arthritis (RA) patients have shown a constant deterioration of joint integrity [1,2]. However, treatment with traditional disease-modifying antirheumatic drugs (DMARDs) alone or in combinations [3,4] with glucocorticoids [5] as well as with biologic agents [6-9] has been shown to retard the progression of joint damage. Early therapy with combinations of conventional DMARDs has been shown to retard

* Correspondence: vappu.rantalaiho@uta.fi
[1] Department of Internal Medicine, Centre for Rheumatic Diseases, Tampere University Hospital, PO Box 2000, FI-33521 Tampere, Finland
Full list of author information is available at the end of the article

the radiologic progression of RA for a period of up to 5 years [4,10], but the effects of initial aggressive DMARD therapy on radiologic prognosis after that are unknown.

We previously demonstrated that early RA patients treated with a combination of DMARDs (methotrexate, sulfasalazine, and hydroxychloroquine with prednisolone) reached, at 2 years, more often clinical remission [3] and had less radiographic progression at 2 years [3] and at 5 years [10] than did patients initially treated with a single DMARD. We also reported that, at 11 years, most patients in both treatment groups had low disease activity and well-preserved function, but the combination DMARD-group patients reached remission more often than did those treated initially with a single DMARD [11].

In this study, we explored the effects of initial treatment strategy on the long-term radiographic findings at 11 years.

Materials and methods

Patients

From April 1993 to May 1995, 199 DMARD-naïve patients with recent-onset RA were admitted to this randomized study comparing the efficacy and tolerability of treatment with either a combination of DMARDs (starting with methotrexate, sulfasalazine, and hydroxychloroquine with prednisolone; FIN-RACo strategy) or a single DMARD (initially sulfasalazine with or without prednisolone; SINGLE strategy). The treatment was targeted toward remission in all patients. After 2 years, the treatment of RA was unrestricted, but still aiming at remission. Thus, regardless of the original randomization group, the patients could be treated liberally with DMARDs, biologic agents, glucocorticoids, and with their combinations, as clinically indicated and tolerated. Conversely, in long-term remission the protocol required drug doses to be reduced and eventually tapered off. The patient-selection criteria and the study design were described in detail earlier [3,10,11].

Radiologic assessment

Hands and feet of all patients were radiographed at baseline and at 2, 5, and 11 years. Hip, knee, elbow, and shoulder joints of the patients were radiographed at 11 years in 13 study centers; in two study centers, only clinically symptomatic large joints were radiographed. Total joint replacements were counted from the radiographs as well as from the patients' medical records. The radiographs were assessed by the same experienced radiologist (LL), who was blinded to the clinical data but aware of the order of the radiographs. The radiographs of hands and feet were scored according to the method of Larsen *et al.* [12], with a range from 0 to 200. The large joints were also scored according to the method of Larsen [12], and a score of ≥2 was considered to indicate erosive disease.

Clinical assessments were performed by the treating rheumatologist. DMARD strategies used between years 2 and 11 were carefully elucidated based on the patient's self-report and his or her medical records [11].

Ethical considerations

The study was performed according to the principles of the Declaration of Helsinki. The protocol was approved by the national health authorities and ethics committees in all 18 participating hospitals. All patients gave written informed consent.

Statistical methods

The data are presented as means with standard deviations (SDs), medians with interquartile ranges (IQRs), or counts with percentages. Statistical comparison between groups was made by *t* test, permutation test, χ^2 test, or the Fisher Exact test, when appropriate. The 95% confidence intervals (95% CIs) for the Larsen score are obtained by bias-corrected bootstrapping due to the skewed distribution. The difference in crude changes in Larsen score between the groups was tested by a permutation test. A random coefficient model with bootstrapped standard errors was adapted to analyze the progression of the Larsen score during 11 years and to compare the groups in time. An ordered logistic regression analysis was used to estimate the prediction of achieving radiologic progression. The adjusted risk ratio (RR) between the groups for having no erosive changes in large joints was estimated by a generalized linear model (log link), with presence of erosion in hands or feet at baseline as covariate. A time-to-event analysis based on the product-limit estimate of the cumulative "survival" function (Kaplan-Meier) was used to describe the time to the first total joint replacement. A log-rank test was used to identify any survival difference between the groups.

Results

Of the 199 patients originally randomized to the study, 195 started treatment, 97 in the FIN-RACo group, and 98, in the SINGLE group. At the 11-year visit, 68 patients were assessed in the FIN-RACo group, and 70, in the SINGLE group; the patients' baseline demographic and clinical characteristics were comparable [11]. In total, 130 patients had radiographs of hands and feet available at baseline and at 11 years, 65 cases in each group.

A trend toward a higher mean (range) Larsen score at baseline was found in the SINGLE group compared with the FIN-RACo group: 5 (0 to 30) versus 3 (0 to 25) (P = 0.069). Furthermore, the dropout cases in the FIN-RACo group had a higher mean ± SD Larsen score at baseline than did the completers: 6 ± 9 versus 3 ± 6 (P = 0.037). In the SINGLE group, the baseline Larsen scores did not dif-

fer between the dropouts and the completers: 3 ± 5 versus 5 ± 7 (P = 0.22).

The cumulative percentages of Larsen scores in both groups are shown in Figure 1. One outlier in the FIN-RACo group had progressed to almost a maximum score after 11 years. Despite active combination DMARD treatment, this patient had had high disease activity and HAQ score throughout the follow-up, and by 11 years, also had damage in large joints as well as one total joint replacement.

The mean Larsen scores of hands and feet at baseline and at 2, 5, and 11 years in both groups are shown in Figure 2. The crude mean change from baseline to 11 years in Larsen score was 17 (95% CI, 12 to 26) in the FIN-RACo group and 27 (95% CI, 22 to 33) in the SINGLE group (P = 0.037). When using all time points (0, 2, 5, and 11 years) and adjusting for Larsen score at baseline, the progression of Larsen score differed statistically significantly between the groups (P = 0.021, for Time-by-Group interaction effect), with the FIN-RACo group having on average lower progression (P < 0.001, for Group-Effect) (Figure 2a). In an ordered logistic regression analysis, the extent of joint-damage progression in hands and feet at 11 years was predicted by the presence of serum rheumatoid factor at baseline and by the single-treatment strategy for the first 2 years (Table 1).

The crude mean change from baseline to 11 years in Larsen score was 10 (95% CI, 6 to 16) in patients who had been in remission at 1 year and 25 (95% CI, 21 to 31) in patients who had not been in remission at 1 year (P = 0.001). When using all time points (0, 2, 5, and 11 years) and adjusting for Larsen score at baseline, the progression of Larsen score differed statistically significantly between the patients in remission and not in remission at 1 year (P < 0.001, for Time-by-Group interaction effect), with the patients in remission at 1 year having on average lower progression (P < 0.001, for Group-Effect) (Figure 3).

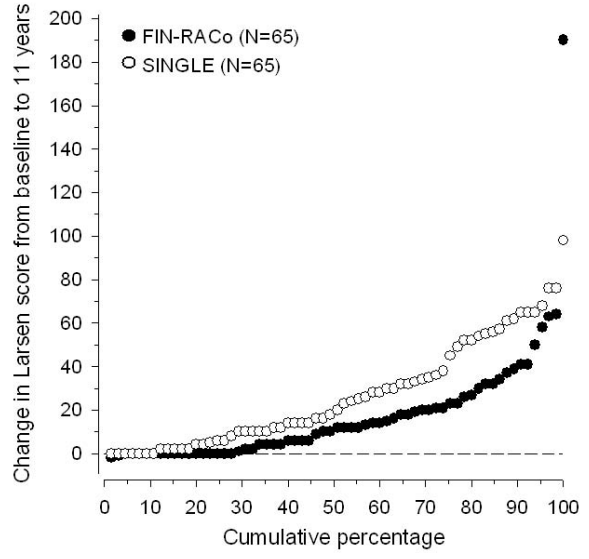

Figure 1 The cumulative percentage of increase in Larsen score from baseline to 11 years in patients initially randomized to receive a combination (FIN-RACo) of disease-modifying antirheumatic drugs (DMARDs) or a single DMARD (SINGLE).

At 11 years, 52 and 54 patients in FIN-RACo and in SINGLE groups, respectively, had all the large joints radiographed. In FIN-RACo and SINGLE groups, 87% (95% CI, 74 to 94) and 72% (95% CI, 58 to 84), respectively, of these patients had no erosive changes in large joints at 11 years (RR, 1.22 (95% CI, 0.99 to 1.50)). The number of damaged large joints (Larsen score, ≥2) did not differ between the groups (Table 2).

Nine patients (four in the FIN-RACo and five in the SINGLE group) had altogether 12 total joint replacements (six knees and six hips). Of these, two arthroplasties had been performed because of primary osteoarthrosis of the knee, and one, because of hip fracture. The occurrence of total joint replacements did not differ between the FIN-RACo and the SINGLE treatment groups: 6% (95% CI, 2 to 16) versus 8% (95% CI, 3 to 18) (P = 0.73) during the follow-up.

Treatment strategies used between 2 to 11 years were reported previously [11]. In both groups, the patients in the tertile of the lowest radiologic progression in hands and feet from year 2 to year 11 (change in Larsen score, 0 to 1) had received significantly shorter periods of combination-DMARD treatments between years 2 and 11 than did the patients with intermediate (change in Larsen score, 2 to 17) or high (change in Larsen score, ≥18) progression rates (P = 0.001 for linearity in both treatment groups) (Figure 4). A similar trend was found for biologic treatments in the entire study population; 14 patients (11%) had received TNF-inhibitors; of these, one had low; five, intermediate; and eight, high radiographic progression between years 2 and 11.

Discussion

The main finding of the present study is that targeting to remission with traditional DMARDs and tight clinical controls results in low radiologic progression in most RA patients. Still, patients treated initially with the FIN-RACo strategy during the first 2 years have less radiographic damage in small joints, even in long term than did those treated initially with DMARD monotherapy.

Less radiographic damage is found in RA patients at present than during previous decades [13]. In our study, both treatment arms had excellent radiologic small-joint outcome compared with historic cohorts. In a previous Finnish cohort of 103 patients with early RA, beginning in the 1970 s, the radiologic progression was steepest

Table 1: Ordered logistic regression analysis for radiologic progression at 11 years

Variable at baseline	Odds ratio (95% CI)	*P* value
Female sex	1.74 (0.84 to 3.60)	0.13
Age, years	0.99 (0.96 to 1.02)	0.60
Disease duration before diagnosis, months	1.02 (0.94 to 1.10)	0.68
Rheumatoid factor positivity	3.17 (1.45 to 6.92)	0.004
Erythrocyte sedimentation rate	1.01 (0.99 to 1.02)	0.33
Larsen score	0.99 (0.94 to 1.05)	0.77
Initial randomization group		0.016
FIN-RACo	1.00 (reference)	
SINGLE	2.39 (1.78 to 4.84)	

Radiologic progression in hands and feet was determined according to the tertiles of Larsen score changes (categories 0 to 1, 2 to 17, and ≥18). FIN-RACo, study group treated for the first 2 years with a combination of three disease-modifying antirheumatic drugs, initially methotrexate, sulfasalazine, and hydroxychloroquine, with prednisolone; SINGLE, study group treated for the first 2 years with one disease-modifying antirheumatic drug, initially sulfasalazine, with or without prednisolone.

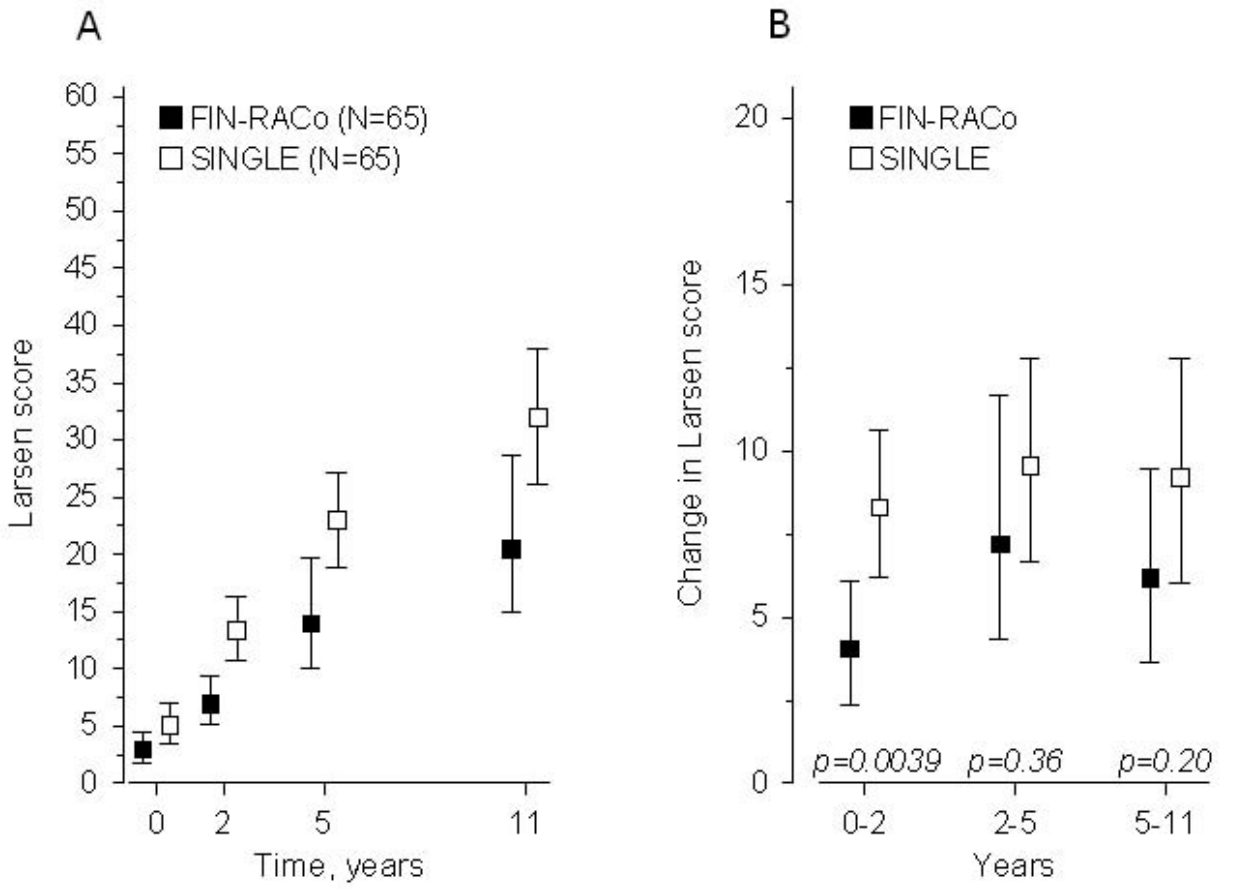

Figure 2 The crude mean Larsen scores of hands and feet at baseline and at 2, 5, and 11 years in patients initially randomized to receive a combination (FIN-RACo) of disease-modifying antirheumatic drugs (DMARDs) or a single DMARD (SINGLE). **(a)** Included are the subjects scored at 11 years (two patients in each group did not have scores at 5 years). Values are expressed as the mean and 95% confidence interval. **(b)** The mean changes in Larsen score during years 0 to 2, 2 to 5, and 5 to 11, according to the initial treatment groups.

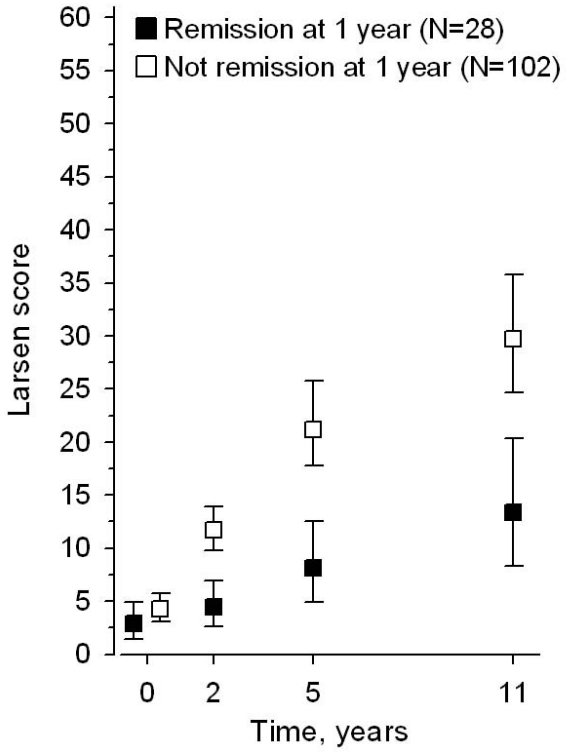

Figure 3 The crude mean Larsen scores of hands and feet at baseline, and at 2, 5, and 11 years in patients who had been in remission at 1 year and in patients who had not been in remission at 1 year. Included are the subjects scored at 11 years (two patients in each group did not have scores at 5 years). Values are expressed as the mean and 95% confidence interval.

during the first 8 years but continued throughout the follow-up of 20 years [1]. In that cohort, the mean ± SD Larsen score at 3 years was 27 ± 21, and at 15 years, 78 ± 49. Thus, after 3 years of RA, the historic patients had comparable amounts of radiographic damage to the patients of the present study at 11 years. In a Swedish cohort starting in 1985, 181 patients with conservatively treated early RA had, at 10 years, a median Larsen score of 54 (IQR, 28 to 80) [2], thus double the Larsen score of our patients at 11 years. These findings are in accordance with those of Finckh *et al.* [13], who found that the radiographic prognosis of RA has improved during the past decades parallel to more active treatments.

Even though most patients had excellent radiographic results at 11 years, the patients treated with the FIN-RACo strategy had significantly lower increases in the median Larsen score from baseline to 11 years than did the SINGLE patients, and besides the presence of rheumatoid factor, only the initial SINGLE treatment predicted the radiographic progression at 11 years in the ordered logistic regression analysis. The main difference between the groups had developed during the first 2 years; after that, both groups progressed similarly. For unknown reasons, the dropout patients in the FIN-RACo group had a higher Larsen score at baseline than did those cases who completed the study. Thus, in the completers of the FIN-RACo group, a trend toward a lower Larsen score at baseline was seen compared with the SINGLE group completers. At worst, this fact may bias the study. However, in the statistical analysis adjusted with baseline Larsen score, a highly significant difference in radiologic progression was found between the groups. Therefore, we find it justified to conclude that the observed difference between the groups represents rather the results of a more-effective initial DMARD treatment strategy than a biologic bias.

For evaluating the radiographic damage, we used the Larsen score, which has been found to be less sensitive to change than the Sharp/van der Heijde method [14,15]. Conversely, the Larsen method tends to be more specific than the Sharp/van der Heijde method [14], and when the follow up is as long as 11 years, we prefer specificity over sensitivity; it is more important to distinguish clinically relevant from unspecific changes than to find subtle joint-space narrowing. Also, the intraobserver reliability in Larsen score is somewhat better than that of the Sharp/van der Heijde method [15,16], and because we have had the same experienced radiologist scoring the radiographs with the Larsen method throughout the follow-up, we find this method logical. To our knowledge, no other methods exist for evaluating the radiographic progression in large joints besides the Larsen method.

Only 13% of the FIN-RACo and 28% of the SINGLE patients had some radiographic damage in large joints. Few long-term studies of early RA assess large-joint damage, and none of them have a definite treatment protocol. One study, published in 1997, found radiographic damage in large joints in 50% of the patients after 6 years of RA [17]. In a Dutch study, 54% of patients had at least one eroded large joint after 12 years of RA [18]. In the present study, the infrequent destruction of large joints was also reflected in the small number of total joint replacements in both of our treatment groups compared with earlier cohorts [19], even though the follow-up of 11 years is too short to evaluate the final incidence of total joint replacements.

Probably the most important precondition to our excellent results in most patients was the active treatment policy aiming at remission at all time points. Even though recent reports showed that radiologic progression may occur even while the patient appears to be in remission [20], most damage still emerges in clinically inflamed joints [21]. Our results emphasize the importance of early remission for the long-term outcome of the patients. In the present study, the patients who had been in strict remission at 1 year had significantly less radiologic pro-

Table 2: Number (percentage) of RA patients with damage to any or to multiple large joints as well as with uni- or bilateral erosive (Larsen score ≥2) large joints after 11 years of follow-up, by initial randomization group

	Original randomization group			
	FIN-RACo (n = 52)		**SINGLE (n = 54)**	
Damage to any large joint	7 (13%)		15 (28%)	
Damage to multiple (two to three) large joints	5 (10%)		10 (19%)	
Radiographed joint	**Unilateral damage**	**Bilateral damage**	**Unilateral damage**	**Bilateral damage**
Shoulder	0	2 (4%)	4 (7%)	7 (13%)
Elbow	1 (2%)	0	1 (2%)	1 (2%)
Hip	3 (6%)	2 (4%)	4 (7%)	1 (2%)
Knee	3 (6%)	1 (2%)	2 (4%)	0

FIN-RACo, study group treated for the first 2 years with a combination of three disease-modifying antirheumatic drugs, initially methotrexate, sulfasalazine, and hydroxychloroquine, with prednisolone; RA, rheumatoid arthritis; SINGLE, study group treated for the first 2 years with one disease-modifying antirheumatic drug, initially sulfasalazine, with or without prednisolone.

gression throughout the follow-up than did the patients who had not reached remission at 1 year. Remissions were reached more often by the FIN-RACo arm patients than by the SINGLE patients at 2 years [3], as well as at 11 years [11], but patients in both treatment arms had mainly low disease activity and well-preserved function throughout the follow-up [11]. This clinical profile fits the radiologic profile of our study groups well; compared with less aggressively treated patients, both groups were doing well, but the FIN-RACo patients even better.

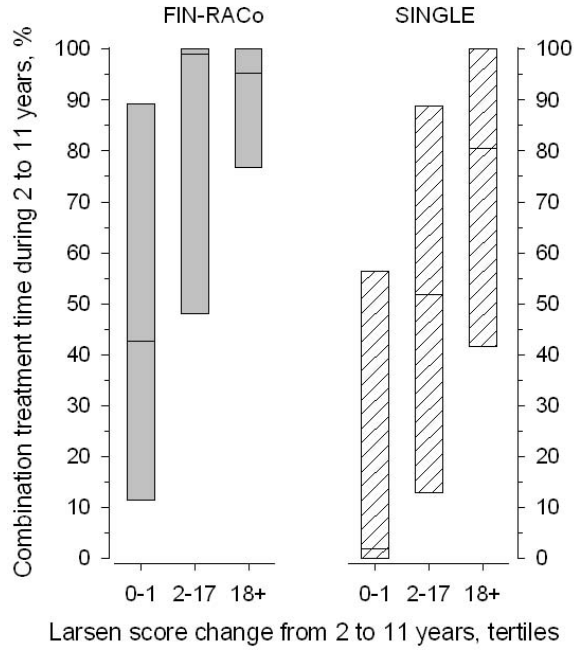

Figure 4 Percentage of treatment time using combination DMARD strategy between year 2 and year 11 in patients of the original randomization groups divided into tertiles, according to change in Larsen score of hands and feet from year 2 to year 11. Values are expressed as median and interquartile range.

We earlier reported that during the liberal treatment phase between years 2 and 11, the use of DMARDs differed between groups, with combination treatments used more often in the original FIN-RACo group [11]. This difference had, however, no impact on the clinical outcome at 11 years. In the FIN-RACo group, the patients who had low disease activity at 11 years had received significantly shorter periods of combination DMARDs between 2 and 11 years than had the patients who had high disease activity at 11 years [11]. Similarly, in the present study, the patients with the least radiologic progression after year 2 had received the shortest periods of combination DMARD strategy after 2 years. These results are in agreement with the fact that in longitudinal observational studies, the cases treated most intensively are the most likely ones to have the most severe disease [22]. And yet, aggressive treatments in established disease do not seem to gain as much effect as they do in early disease. This emphasizes the importance of early, effective treatment and tight control of therapeutic response. Late strengthening of DMARD treatment is not able to reverse the damage already arisen. Nevertheless, it is probable that radiologic progression would have been even steeper had the treatments during the liberal phase been less aggressive.

Glucocorticoids were a part of the FIN-RACo strategy and were allowed in the SINGLE strategy to reach remis-

sion. Because glucocorticoids have been shown to retard radiologic progression [5], it could be hypothesized that their use would explain the difference in Larsen score between the groups. However, the patients treated with the FIN-RACo strategy needed fewer intraarticular glucocorticoid injections and had a smaller cumulative dose of glucocorticoids during the first 2 years than did the SINGLE strategy group [3]. Thus, the better radiologic outcome in the FIN-RACo arm does not seem to depend on the use of glucocorticoids, but rather on the more effective and rapidly working DMARDs during the critical "window of opportunity." Whether the difference between the groups would have been smaller, had the first DMARD in the SINGLE strategy been methotrexate, cannot be answered by this study. However, the SINGLE strategy was not tied to sulfasalazine but to a strategy of using one DMARD at a time, and, during the first 2 years, 52% of patients in the SINGLE group were switched to methotrexate [3].

Conclusions

We conclude that treating RA from the very beginning actively and aggressively with DMARDs, including tight clinical control and aiming for remission, pays off, even in the long run. Further, the patients treated initially with the FIN-RACo strategy manage better than the cases treated actively with the SINGLE strategy. Both small and large peripheral joints are spared. Consequently, the need for joint-replacement operations decreases. Clinical disease activity remains low, functional capacity well preserved, and life expectancy normal [11]. Further studies will reveal whether all this is reflected in the maintenance of working capacity.

Abbreviations

CI: confidence interval; DMARD: disease-modifying antirheumatic drug; FIN-RACo: study group treated for the first 2 years with a combination of three disease-modifying antirheumatic drugs: initially methotrexate: sulfasalazine: and hydroxychloroquine: with prednisolone; HAQ: health assessment questionnaire; IQR: interquartile range; RA: rheumatoid arthritis; RR: risk ratio; SD: standard deviation; SINGLE: study group treated for the first 2 years with one disease-modifying antirheumatic drug: initially sulfasalazine: with or without prednisolone; TNF: tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

VR participated in the acquisition of data, performed the statistical analysis with HK and SJ, and drafted the manuscript. MK, PH, ML-R, and TM belong to the advisory board of the FIN-RACo study, which is responsible for the study design; they also participated in the acquisition of data and helped to draft the manuscript. LL scored the patients' radiographs and participated in drafting the manuscript. HB, KP, and AK participated in the acquisition of data and helped to draft the manuscript. All authors have been involved in drafting the manuscript and have given final approval of the version to be published.

Acknowledgements

The study was supported by the Medical Research Fund of Tampere University Hospital and by the Finnish Society for Rheumatology.

Other members of the FIN-RACo Trial Group contributing to this study during the 11 years are Jari Ahonen, Sinikka Forsberg, Mikko Hakola, Tapani Helve, Kirsti Ilva, Oili Kaipiainen-Seppänen, Markku Kauppi, Reijo Luukkainen, Ilppo Pälvimäki, Kaisa Vuori, and Urpo Yli-Kerttula. The administrative board responsible for the study consists of Timo Möttönen, Martti Nissilä, Markku Hakala, Pekka Hannonen, Marjatta Leirisalo-Repo, and Markku Korpela.

Author Details

[1]Department of Internal Medicine, Centre for Rheumatic Diseases, Tampere University Hospital, PO Box 2000, FI-33521 Tampere, Finland, [2]Helsinki Medical Imaging Center, University of Helsinki, Tukholmankatu 8B, PO Box 20, 00014 Helsinki, Finland, [3]Orton Foundation, Tenholantie 10, 00280 Helsinki, Finland, [4]Medcare Foundation, Hämeentie 1, 44100 Äänekoski, Finland, [5]Jyväskylä Central Hospital, Keskussairaalantie 19, 40620 Jyväskylä, Finland, [6]Helsinki University Central Hospital, Stenbäckinkatu 9, 00290 Helsinki, Finland, [7]Seinäjoki Central Hospital, Hanneksenrinne 7, 60220 Seinäjoki, Finland, [8]Lappeenranta Central Hospital, Valto Käkelän katu 1, 53130 Lappeenranta, Finland, [9]Oulu University Hospital, PO Box 22, 90221 Oulu, Finland and [10]Turku University Hospital, PO Box 52, 20521 Turku, Finland

Received: 26 October 2009 Revised: 18 February 2010
Accepted: 24 June 2010 Published: 24 June 2010

References

1. Kaarela K, Kautiainen H: **Continuous progression of radiological destruction in seropositive rheumatoid arthritis.** *J Rheumatol* 1997, **24:**1285-1287.
2. Lindqvist E, Jonsson K, Saxne T, Eberhardt K: **Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis.** *Ann Rheum Dis* 2003, **62:**611-616.
3. Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, Laasonen L, Julkunen H, Luukkainen R, Vuori K, Paimela L, Blåfield H, Hakala M, Ilva K, Yli-Kerttula U, Puolakka K, Järvinen P, Hakola M, Piirainen H, Ahonen J, Pälvimaki I, Forsberg S, Koota K, Friman C: **Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial: FIN-RACo trial group.** *Lancet* 1999, **353:**1568-1573.
4. Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, van Denderen JC, Westedt ML, Peeters AJ, Dijkmans BA, Jacobs P, Boonen A, van der Heijde DM, van der Linden S: **COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention.** *Arthritis Rheum* 2002, **46:**347-356.
5. Kirwan JR, Bijlsma JW, Boers M, Shea BJ: **Effects of glucocorticoids on radiological progression in rheumatoid arthritis.** *Cochrane Database Syst Rev* 2007:CD006356.
6. St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, Keystone E, Schiff M, Kalden JR, Wang B, Dewoody K, Weiss R, Baker D: **Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial.** *Arthritis Rheum* 2004, **50:**3432-3443.
7. Genovese MC, Bathon JM, Fleischmann RM, Moreland LW, Martin RW, Whitmore JB, Tsuji WH, Leff JA: **Long-term safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis.** *J Rheumatol* 2005, **32:**1232-1242.
8. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL, Spencer-Green GT: **The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment.** *Arthritis Rheum* 2006, **54:**26-37.
9. Westhovens R, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P, Gomez-Reino J, Grassi W, Haraoui B, Shergy W, Park SH, Genant H, Peterfy C, Becker JC, Covucci A, Helfrick R, Bathon J: **Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors.** *Ann Rheum Dis* 2009, **68:**1870-1877.
10. Korpela M, Laasonen L, Hannonen P, Kautiainen H, Leirisalo-Repo M, Hakala M, Paimela L, Blåfield H, Puolakka K, Möttönen T: **Retardation of joint damage in patients with early rheumatoid arthritis by initial**

aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. *Arthritis Rheum* 2004, **50:**2072-2081.

11. Rantalaiho V, Korpela M, Hannonen P, Kautiainen H, Jarvenpaa S, Leirisalo-Repo M, Hakala M, Puolakka K, Julkunen H, Luosujarvi R, Mottonen T: **The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial.** *Arthritis Rheum* 2009, **60:**1222-1231.
12. Larsen A, Dale K, Eek M: **Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films.** *Acta Radiol Diagn (Stockh)* 1977, **18:**481-491.
13. Finckh A, Choi HK, Wolfe F: **Progression of radiographic joint damage in different eras: trends towards milder disease in rheumatoid arthritis are attributable to improved treatment.** *Ann Rheum Dis* 2006, **65:**1192-1197.
14. Bruynesteyn K, van der Heijde D, Boers M, Saudan A, Peloso P, Paulus H, Houben H, Griffiths B, Edmonds J, Bresnihan B, Boonen A, van der Linden S: **Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference.** *Arthritis Rheum* 2002, **46:**913-920.
15. Guillemin F, Billot L, Boini S, Gerard N, Odegaard S, Kvien TK: **Reproducibility and sensitivity to change of 5 methods for scoring hand radiographic damage in patients with rheumatoid arthritis.** *J Rheumatol* 2005, **32:**778-786.
16. Sharp JT, Wolfe F, Lassere M, Boers M, Van Der Heijde D, Larsen A, Paulus H, Rau R, Strand V: **Variability of precision in scoring radiographic abnormalities in rheumatoid arthritis by experienced readers.** *J Rheumatol* 2004, **31:**1062-1072.
17. Kuper HH, van Leeuwen MA, van Riel PL, Prevoo ML, Houtman PM, Lolkema WF, van Rijswijk MH: **Radiographic damage in large joints in early rheumatoid arthritis: relationship with radiographic damage in hands and feet, disease activity, and physical disability.** *Br J Rheumatol* 1997, **36:**855-860.
18. Drossaers-Bakker KW, Kroon HM, Zwinderman AH, Breedveld FC, Hazes JM: **Radiographic damage of large joints in long-term rheumatoid arthritis and its relation to function.** *Rheumatology (Oxford)* 2000, **39:**998-1003.
19. Wolfe F, Zwillich SH: **The long-term outcomes of rheumatoid arthritis: a 23-year prospective, longitudinal study of total joint replacement and its predictors in 1,600 patients with rheumatoid arthritis.** *Arthritis Rheum* 1998, **41:**1072-1082.
20. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, Hensor E, Wakefield RJ, O'Connor PJ, Emery P: **An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis.** *Arthritis Rheum* 2008, **58:**2958-2967.
21. Boers M, Kostense PJ, Verhoeven AC, van der Linden S: **Inflammation and damage in an individual joint predict further damage in that joint in patients with early rheumatoid arthritis.** *Arthritis Rheum* 2001, **44:**2242-2246.
22. Landewe RB: **The benefits of early treatment in rheumatoid arthritis: confounding by indication, and the issue of timing.** *Arthritis Rheum* 2003, **48:**1-5.

doi: 10.1186/ar3060
Cite this article as: Rantalaiho *et al.*, Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial *Arthritis Research & Therapy* 2010, **12**:R122

Trends in Treatment Strategies and the Usage of Different Disease Modifying Antirheumatic Drugs in Early Rheumatoid Arthritis in Finland. Results from a Nationwide Register in Years 2000-2007

Category: Article

Short title: DMARDs in Finland 2000-07

Vappu Rantalaiho[1], Hannu Kautiainen[2], Lauri Virta[3], Markku Korpela[1], Timo Möttönen[4] and Kari Puolakka[5]

[1]Tampere University Hospital, Tampere, Finland; [2]Orton Foundation, Helsinki, Finland and Jyväskylä Central Hospital, Jyväskylä, Finland; [3]Social Insurance Institution, Turku, Finland; [4]University of Turku and Turku University Hospital, Finland; [5]Lappeenranta Central Hospital, Lappeenranta, Finland

The study was supported by the Medical Research Fund of Tampere University Hospital, by the Finnish Society for Rheumatology and by the Medcare Foundation.

Corresponding author: Vappu Rantalaiho, MD, Department of Internal Medicine, Centre for Rheumatic Diseases, Tampere University Hospital, PO BOX 2000, FI-33521 Tampere, FINLAND. Email: vappu.rantalaiho@pshp.fi. Telephone: +358 3 31165669, Fax + 358 3 311 64369.

Abstract

Objectives. To determine disease modifying antirheumatic drugs (DMARDs) currently used by Finnish rheumatologists to treat early rheumatoid arthritis (RA).

Methods. Information on sex, date of birth, and date of special medicine reimbursement decision for all new RA patients was collected from a nationwide register maintained by the Social Insurance Institution (SII) during the time period from 1.1.2000 to 31.12.2007. Patient cohorts were registered in 2-year time periods (2000-01, 2002-03, 2004-05, 2006-07) and disease modifying antirheumatic drugs (DMARDs) purchased by the patient cohorts during the first year after the date of reimbursement decision for RA were registered. The frequencies of early drug treatment strategies (combination of DMARDs, single DMARD or no DMARD) were evaluated.

Results. A total of 14 878 (68.0% female, 62.6% RF-positive) patients were identified. Between years 2000-01 the most commonly used treatment strategy for early RA during the first 3 months was single DMARD treatment (56.1%) and the most commonly used DMARD during the first year was sulfasalazine (63.0%), while between years 2006-07 the respective treatments were combination DMARDs (55.3%) and methotrexate (69.0%). The change in treatment strategies as well as in DMARDs used was highly significant (P <0.001 for linearity). At the end of the study period only 4.9% of the patients with early RA were not receiving DMARDs during the first three months.

Conclusions. Currently, combination therapy including methotrexate is the most commonly prescribed treatment strategy for early RA in Finland. During the present millennium more and more active drug treatments have been taken into practice.

Introduction

When untreated, rheumatoid arthritis (RA) causes continuing destruction of the joints in most patients. Impaired function leads to need for hospitalizations and to decreased working capacity, both of which cause expenses for the individual and for the society. Diseases modifying antirheumatic drugs (DMARDs) reduce inflammation, prevent structural damage and thus improve function in RA. Early and aggressive therapy with tight clinical controls aiming at the lowest possible disease activity has been shown to be effective in reaching these goals.(1-3)

Several national recommendations have been given on the treatment of RA(4-8) but whether clinical practice is in line with these guidelines, is unknown. The Finnish Current Care guideline(4) recommends as the first medication in active early RA either methotrexate or a combination of methotrexate, sulfasalazine, hydroxychloroquine, and low dose glucocorticoids (the FIN-RACo combination).(9) Other DMARDs may be used according to individual judgment. Biological treatments are indicated if the arthritis continues active (swollen joints ≥ 6 and tender joints ≥ 6 and either an ESR ≥ 30 mm/h or a CRP ≥ 28 mg/l or morning stiffness ≥ 45 minutes) in spite of a DMARD combination, which has included methotrexate.

In this nation-wide register-study we wanted to assess which DMARDs and treatment strategies are currently used to treat early RA in Finland and whether the guidelines are followed.

Methods

Finland has a general sickness insurance covering the entire population, and all permanent residents are issued a personal health insurance card. The costs of medicines prescribed by a doctor for the treatment of an illness are more or less reimbursed by the Social Insurance Institution (SII). The basic medicine reimbursement rate is 42% of the price but patients with certain chronic and severe diseases are entitled to a special reimbursement of medications if their condition meets predefined criteria. The patients with chronic inflammatory rheumatic disorders can be granted the

special reimbursement of 72% for antirheumatic drugs. To establish entitlement, the patient must submit to the SII a medical certificate based on examinations performed by a specialist-level health care unit or issued by a specialist. The medical certificate must include information on proper diagnostic procedures, an ICD-10 diagnosis, and a treatment plan according to a good clinical practice. The certificates are reviewed by an insurance physician of SII before the special reimbursement can be granted. The administrative process usually takes a couple of weeks. Up to three months' supply of medicines can be reimbursed at one transaction. Practically all Finnish patients with antirheumatic medications receive the reimbursement decision since it is economically very much in the patients' interest and in the rare occasions when the reimbursement decision does not exist, the pharmacists generally encourage the patients to request it.

Patient cohort. All medicine reimbursement decisions are gathered in a nationwide register maintained by the SII. From that register we assessed data gathered from 1.1.2000 to 31.12.2007, and collected information of patients who, for the first time in their life, had been granted a special reimbursement of medications for rheumatoid factor (RF) -positive (ICD-10 diagnosis M05) or RF-negative RA (M06). The information included sex, date of birth, and the date of reimbursement decision (index day).

The SII maintains a prescription register on the drugs purchased from pharmacies and reimbursed either according to the basic or the special rate. In the register, drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification (10). The register includes also the amount of the drug as well as the date of purchase. From this register, we gathered the data on the drugs purchased by the patient cohort for 31 days before the index day (to include medication possibly purchased before the reimbursement decision) and for 31 days, for 91 days, and for one year after the index day. The first-month and first-year treatments were analyzed in 2-year time periods (2000-01, 2002-03, 2004-05, 2006-07) and any change in drugs over this time recorded. The purchase of initial glucocorticoids was assessed only between years 2000 and 2005

since prednisolone 5 mg tablets were not reimbursed in Finland between 1.1.2006 and 30.11.2007. Further, we investigated the early drug treatment strategy up to 3 months from the index day - no DMARD, single conventional DMARD, combination of conventional DMARDs, or treatment including TNF-inhibitors – and the change in strategy over time. The intravenous drugs given and reimbursed by hospitals and outpatient clinics are not registered by the SII. Consequently, our study does not include infliximab or other infusion-based biologic therapies.

Ethical considerations. There was no legal requirement for approval by an ethics committee, since only unidentifiable register data were used and patients were not contacted.

Statistical methods. Statistical comparisons between groups were made by using analysis of variance (ANOVA) and chi-square test. Statistical significance for hypotheses of linearity was evaluated by Cochran-Armitage test.

Results

Information of a total of 14 878 patients was assessed. Of these, 9314 (62.6%) had received their reimbursement decision on grounds of RF positive RA and the rest for RF negative disease. The mean (SD) age in the entire patient cohort was 56 (15) years and 10 117 (68.0%) patients were female.

Throughout all time periods (2000-01, 2002-03, 2004-05 and 2006-07), methotrexate, sulfasalazine and hydroxychloroquine were the three most prescribed DMARDs during the first year of RA; all the other DMARDs had been prescribed to a substantially smaller percentage of patients (Table 1). Sulfasalazine had been the most often used DMARD in 2000-01, but after that its use had decreased and that of hydroxychloroquine and especially of methotrexate had increased (Table 1). A total of 69% of new patients with RA received methotrexate during the first year of drug treatment in 2006-07.

Medication	Years				P for linearity
	2000-01 N=3739 N (%)	2002-03 N=3880 N (%)	2004-05 N=3631 N (%)	2006-07 N=3628 N (%)	
Medication during the first 12 months					
Methotrexate	1639 (43.8)	2079 (53.9)	2330 (64.2)	2505 (69.0)	<0.001
Sulfasalazine	2355 (63.0)	2355 (60.7)	2127 (58.6)	1975 (54.4)	<0.001
Hydroxychloroquine	1879 (50.2)	2045 (52.7)	2056 (56.6)	2169 (59.8)	<0.001
Sodium aurothiomalate	333 (8.9)	204 (5.3)	139 (3.8)	86 (2.4)	<0.001
Auranofin	200 (5.3)	150 (3.9)	76 (2.1)	49 (1.3)	<0.001
Leflunomide	65 (1.7)	140 (3.6)	184 (5.1)	179 (4.9)	<0.001
Azathioprine	51 (1.4)	53 (1.4)	49 (1.3)	40 (1.1)	0.34
Ciclosporin	52 (1.4)	51 (1.3)	43 (1.2)	28 (0.8)	0.012
Podophyllotoxin	19 (0.5)	17 (0.4)	19 (0.5)	28 (0.8)	0.11
Penicillamine	2 (0.1)	3 (0.1)	0 (0)	0 (0)	0.12
Cyclophosphamide	1 (0.0)	7 (0.2)	4 (0.1)	3 (0.1)	0.73
Adalimumab/Etanercpt	0 (0)	13 (0.3)	58 (1.6)	38 (1.0)	<0.001

Table 1. Proportions of patients using various antirheumatic drugs during the first year of drug treatment.

We then studied the use of methotrexate, sulfasalazine and hydroxychloroquine alone or in combinations up until 31 days after the index day, i.e., obviously as the very first DMARD or DMARDs (Table 2). As this very early treatment, the use of methotrexate alone or in combinations increased from 23.5% of the patients in 2000-01 to 56.0% in 2006-07 ($p<0.001$). Also the use of glucocorticoids as a very early treatment of RA increased during the follow-up (Table 2).

Medication	Years				P for linearity
	2000-01 N=3739 N (%)	2002-03 N=3880 N (%)	2004-05 N=3631 N (%)	2006-07 N=3628 N (%)	
Single treatment					
Methotrexate	352 (9.4)	392 (10.1)	464 (12.8)	708 (19.5)	<0.001
Sulfasalazine	1113 (29.8)	1083 (27.9)	789 (21.7)	641 (17.7)	<0.001
Hydroxychloroquine	415 (11.1)	368 (9.5)	296 (8.2)	227 (6.3)	<0.001
Combination treatment					
Methotrexate and hydroxychloroquine	148 (4.0)	242 (6.2)	312 (8.6)	502 (13.8)	<0.001
Methotrexate and sulfasalazine	155 (4.1)	137 (3.5)	187 (5.2)	248 (6.8)	<0.001
Sulfasalazine and hydroxychloroquine	229 (6.1)	259 (6.7)	225 (6.2)	249 (6.9)	0.34
Methotrexate, sulfasalazine and hydroxychloroquine	226 (6.0)	324 (8.4)	481 (13.2)	576 (15.9)	<0.001
Glucocorticoids	1379 (36.9)	1591 (41.0)	1637 (45.1)	N.A.	<0.001

Table 2. Proportions of the most commonly used antirheumatic medications (methotrexate, sulfasalazine, hydroxychloroquine) in single and combination strategies and the proportion of patients with glucocorticoids during the first month of drug treatment. The use of glucocorticoids could not be assessed after year 2005 because of change in drug reimbursement policy.

During the first 3 months the treatments were generally further intensified (Table 3). Only 6.3 % of all patients had not purchased DMARDs during the first 3 months and this non-compliance decreased significantly from 2000-01 to 2006-07 (Table 3). During the study period the use of early single DMARD strategy decreased and the use of early combination DMARD strategy increased (Table 3). Combination strategy was prescribed more often to seropositive and to younger patients than single DMARD strategy, whereas both genders were treated equally (Table 4).

Medication	Years				P for linearity
	2000-01 N=3739 N (%)	2002-03 N=3880 N (%)	2004-05 N=3631 N (%)	2006-07 N=3628 N (%)	
No DMARDs	240 (6.4)	273 (7.0)	245 (6.7)	179 (4.9)	0.0072
Single therapy	2097 (56.1)	2034 (52.4)	1606 (44.2)	1427 (39.3)	<0.001
Combination therapy*	1402 (37.5)	1572 (40.5)	1765 (48.6)	2006 (55.3)	<0.001
Adalimumab/Etanercept					
only TNF-inhibitor	0 (0.0)	0 (0.0)	3 (0.1)	4 (0.1)	ND
and one DMARD	0 (0.0)	1 (0.0)	5 (0.1)	4 (0.1)	ND
and DMARD combination	0 (0.0)	0 (0.0)	7 (0.2)	8 (0.2)	ND

*Two or more DMARDs

Table 3. Proportions of treatment strategies during the first 3 months of RA treatment.

Variables	No DMARDs N=944	Single therapy N=7174	Combination therapy N=6760	P value
Female, n (%)	629 (66.6)	4867 (67.8)	4623 (68.4)	0.49
Age, mean (SD)	54 (15)	58 (16)	55 (14)	<0.001
Rheumatoid factor present, n (%)	556 (58.9)	4207 (58.6)	4556 (67.4)	<0.001

Table 4. Association of gender, age and rheumatoid factor with the early (up to 3 months) drug treatment strategy

The use of the FIN-RACo combination (methotrexate, sulfasalazine and hydroxychloroquine) as initial treatment increased throughout the study period (Table 2). During 2006-07 it was prescribed to 20.3 % of the patients with recent-onset RA within the first 3 months (Figure 1).

The use of adalimumab and etanercept during the first 3 months or even during the first year of RA therapy remained extremely rare throughout the study period (Table 1, Table 3).

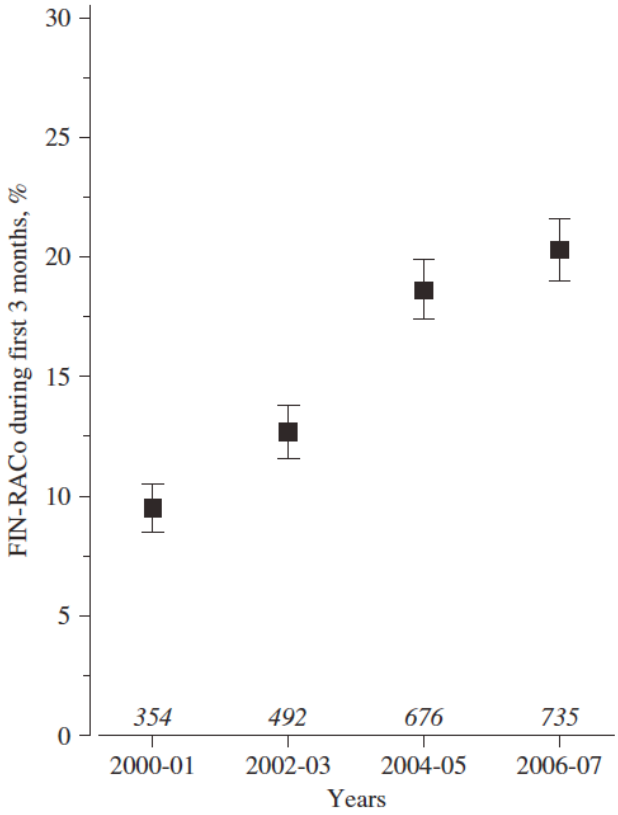

Figure 1. Proportion of the FIN-RACo combination (hydroxychloroquine, sulfasalazine, and methotrexate) strategy in the treatment of early RA in Finland.

Discussion

In this national register study of practically all Finnish patients with a recent diagnosis of RA between years 2000 and 2007, we found that almost all patients were prescribed a DMARD during the first 3 months after diagnosis. In the beginning of the study period less than 7 percent of the patients were receiving no DMARDs during the first 3 months and by the end of the study this proportion had decreased to less than 5%. Single DMARD was the most often used initial strategy in the beginning of the study period but during the follow up it gave way to combination DMARDs with especially the FIN-RACo combination gaining increasing support. Methotrexate substituted for sulfasalazine as the most used DMARD. Also the use of glucocorticoids early in RA increased somewhat. All these features of active treatment policy are in accordance with national guidelines(4) and with international trends.(11)

Worldwide, the treatment of RA has changed enormously during the past decades.(11) Despite the new medications made available during the recent years, the most revolutionary change has occurred in the rheumatologists' way of thinking; the importance of starting treatments early and of aiming at the lowest possible disease activity has been acknowledged. National guidelines for the treatment of early RA have been published at least in the Netherlands,(5) France,(6) UK,(8) US(7) and Finland.(4) However, implementing recommendations or positive study results to everyday practice is not always self-evident,(12-15) thus studies on current DMARD strategies are needed.

Different methods can be used to assess the use of DMARDs. Interviewing rheumatologists has some disadvantages.(16-19) The respond rate is seldom high and it is possible that physicians report more idealistic treatment strategies than the ones they actually use. When studying cohorts of RA patients the results may be somewhat misleading since the patients are treated by specialists and thus in many countries represent only a minority of RA patients.(12, 20-25) Large register based cohorts of patients give a more realistic view to the current DMARD policy; even though the patient populations may be heterogeneous in terms of disease durations.(13, 26, 27) So far the results of register studies have illustrated rather a nihilistic view; the use of DMARDs has been surprisingly sparse, only 13%(26) to 50%(27) of the RA patients were receiving DMARDs. This may partly be explained by the fact that these studies were carried out in an earlier era and that the majority of patients were treated by non-rheumatologists.

When comparing our results with those from other countries, the studies not extending to this millennium have merely a historical relevance. The results of the more recent studies show that the majority of rheumatologists prefer methotrexate(19, 22) or either methotrexate or sulfasalazine(16) as the first DMARD in early RA, which is in line with our findings, as is the finding that more aggressive strategies are applied to younger than to older RA patients.(18) In a large register study between years 1987 and 2002, 34 364 patients with RA of various duration were identified from the

UK national database (General Practice Research Database, GRRD) and DMARDs prescribed to them were assessed. Only 50% of the patients were prescribed at least one DMARD during the study period, most often sulfasalazine (46.3%) or methotrexate (31.4%), the use of the latter having increased 17-fold during the study period while the use of intramuscular gold had decreased.(27) A single-institute-based Japanese cohort of 7512 patients with established RA from October 2000 to April 2006 showed that the use of DMARDs increased from 82.18% to 89.60%, the frequency of methotrexate users increased from 33.9% to 58.7% and that the average dosage of methotrexate also increased.(25) In a more recent Swedish study, register data of disease characteristics and DMARD prescriptions were collected from 2584 patients with early RA at 19 hospitals between 1997 and 2001. Prescriptions of DMARDs, especially of methotrexate, increased during the study period, more in university or county hospitals than in district hospitals. The proportion of patients with early RA not prescribed any DMARDs decreased from 32.2% to 14.9% during the follow up.(20) Between 2002 and 2007 in the UK, a cohort of 691 patients with early RA was collected and followed up for at least 3 months. Initially 97 % of the patients were prescribed a DMARD; 91 % of these received monotherapy, mainly methotrexate (51 %) or sulfasalazine (41 %), and 9 % received combination therapy. Treatment intensification was required in 33 % of the patients of whom 52 % got sequential monotherapy and 48 % step-up combination therapy.(15) Thus, there are marked national variations in the tradition of treating RA, but worldwide, the strategy has changed towards a more active one.

Naturally, our results can not be generalized to other countries. However, they show that treating early RA according to the modern guidelines is possible despite the nihilistic view given by earlier cohort studies.(13, 26, 27) Finnish rheumatologists have traditionally treated RA aggressively;(28, 29) the active strategy having it’s roots in the 1970s.(30) Prescribing DMARD combinations has gained increasing national support after the publication of the favorable results of the FIN-RACo study,(2, 9, 31, 32) which all the large rheumatology centers in Finland participated

in. That might also explain why the implementation of this strategy to everyday practice has not faced such problems as the COBRA strategy has in Holland.(14) Moreover, as the doctor's certificate for medicine reimbursement decision needs to be done by a specialist, the vast majority of patients are seen by rheumatologists who initiate the treatment and also, according to the national guideline, follow the patient up for at least one year. Even though some local variation in the availability of rheumatology services exists, so far Finland has had enough rheumatologists to handle this task.

Thus, a prerequisite for inclusion to our cohort was RA diagnosis made by a rheumatologist. We have, however, no data about the fulfillment of the ACR classification criteria for RA. Therefore it is possible that that some patients did not fulfill the ACR criteria for RA,(33) but were assumed by a rheumatologist to represent very early RA because of anti-cyclic citrullinated peptides or some other features and institution of DMARDs was deemed necessary. In RA, ample evidence shows the importance of early institution of remission-targeted drug treatment for prevention of disease's adverse consequences(2, 34) and recent data suggest that treatment of early arthritis with DMARDs is beneficial even before the fulfillment of the ACR classification criteria for RA.(35, 36)

We have no information on the patients' disease activity or functional ability. Obviously, the patients with active disease are more likely to be prescribed aggressive treatments than the ones with mild disease,(17) in which also the evidence base for aggressive treatment is far flimsier than in active RA. On the other hand, different medications may be contraindicated for various – good – reasons. Especially older patients are more likely to have comorbidities and to be more prone to side effects than younger patients, thus the age of the patient is likely to affect the choice of the treatment strategy in RA.(18) Inevitably these real life variables have affected also our results; this could be seen for example from the fact that combination treatments were more often given to seropositive and to younger patients. Still, despite this "natural" restriction of the treatment choices, the vast majority of Finnish patients with early RA were treated actively.

To summarize, we found that almost all Finnish patients with early RA received DMARDs – most of them methotrexate - within the first 3 months of treatment. Presumably the results of the FIN-RACo study have encouraged Finnish rheumatologists to increasing use of DMARD combinations as the initial treatment. Whether this active strategy is reflected to better maintenance of functional and working capacity, decreased need of reconstructive surgery and reduction in pre-term mortality will be revealed by further studies.

Funding and acknowledgements

The study was supported by the Medical Research Fund of Tampere University Hospital, by the Finnish Society for Rheumatology and by the Medcare Foundation.

We acknowledge MSc Salme Järvenpää from the Medcare foundation for helping in the statistical analysis.

References

1. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263-9.
2. Puolakka K, Kautiainen H, Möttönen T, Hannonen P, Korpela M, Hakala M, et al. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. Arthritis Rheum 2005;52:36-41.
3. Rantalaiho V, Korpela M, Hannonen P, Kautiainen H, Järvenpää S, Leirisalo-Repo M, et al. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: The eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. Arthritis Rheum 2009;60:1222-31.
4. Rheumatoid arthritis (online). Current Care Guideline. Article in Finnish. Working group set up by the Finnish Medical Society Duodecim and the Finnish Society for Rheumatology. Helsinki: The Finnish Medical Society Duodecim, 2003 (retrieved August 13 2009). Available on internet: www.kaypahoito.fi.

5. Bijlsma JW, Jacobs JW. [The practice guideline 'Rheumatoid arthritis' (first revision) from the Dutch College of General Practitioners: a response from the perspective of rheumatology]. Ned Tijdschr Geneeskd 2004;148:557-8.
6. Le Loet X, Berthelot JM, Cantagrel A, Combe B, De Bandt M, Fautrel B, et al. Clinical practice decision tree for the choice of the first disease modifying antirheumatic drug for very early rheumatoid arthritis: a 2004 proposal of the French Society of Rheumatology. Ann Rheum Dis 2006;65:45-50.
7. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762-84.
8. Deighton C, O'Mahony R, Tosh J, Turner C, Rudolf M. Management of rheumatoid arthritis: summary of NICE guidance. BMJ 2009;338:b702.
9. Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353:1568-73.
10. The WHO Collaborating Centre for Drug Statistics Methodology. Last updated: 2009-03-06 Available on internet: http://www.whocc.no/atcddd/.
11. Sokka T, Envalds M, Pincus T. Treatment of rheumatoid arthritis: a global perspective on the use of antirheumatic drugs. Mod Rheumatol 2008;18:228-39.
12. Kvalvik AG, Aadland HA, Hoyeraal HM, Larsen S. Were the patterns of treatment for rheumatoid arthritis during 1977-1992 consistent with modern clinical guidelines? Scand J Rheumatol 2001;30:61-8.
13. Schmajuk G, Schneeweiss S, Katz JN, Weinblatt ME, Setoguchi S, Avorn J, et al. Treatment of older adult patients diagnosed with rheumatoid arthritis: improved but not optimal. Arthritis Rheum 2007;57:928-34.
14. van Tuyl LH, Plass AM, Lems WF, Voskuyl AE, Dijkmans BA, Boers M. Why are Dutch rheumatologists reluctant to use the COBRA treatment strategy in early rheumatoid arthritis? Ann Rheum Dis 2007;66:974-6.
15. Kiely P, Williams R, Walsh D, Young A. Contemporary patterns of care and disease activity outcome in early rheumatoid arthritis: the ERAN cohort. Rheumatology (Oxford) 2009;48:57-60.
16. Jobanputra P, Wilson J, Douglas K, Burls A. A survey of British rheumatologists' DMARD preferences for rheumatoid arthritis. Rheumatology (Oxford) 2004;43:206-10.
17. Maetzel A, Bombardier C, Strand V, Tugwell P, Wells G. How Canadian and US rheumatologists treat moderate or aggressive rheumatoid arthritis: a survey. J Rheumatol 1998;25:2331-8.
18. Fraenkel L, Rabidou N, Dhar R. Are rheumatologists' treatment decisions influenced by patients' age? Rheumatology (Oxford) 2006;45:1555-7.
19. Maravic M, Berge C, Daures JP, Boissier MC. Survey of practices regarding management of early rheumatoid arthritis by rheumatologists in France. Clin Exp Rheumatol 2004;22:319-27.
20. Carli C, Ehlin AG, Klareskog L, Lindblad S, Montgomery SM. Trends in disease modifying antirheumatic drug prescription in early rheumatoid arthritis are influenced more by hospital setting than patient or disease characteristics. Ann Rheum Dis 2006;65:1102-5.
21. Saraux A, Berthelot JM, Chales G, Le HC, Thorel J, Hoang S, et al. Second-line drugs used in recent-onset rheumatoid arthritis in Brittany (France). Joint Bone Spine 2002;69:37-42.
22. Sokka T, Pincus T. Contemporary disease modifying antirheumatic drugs (DMARD) in patients with recent onset rheumatoid arthritis in a US private practice: methotrexate as the anchor drug in 90% and new DMARD in 30% of patients. J Rheumatol 2002;29:2521-4.
23. Ward MM. Trends in the use of disease modifying antirheumatic medications in rheumatoid arthritis, 1980-1995: results from the National Ambulatory Medical Care Surveys. J Rheumatol 1999;26:546-50.

24. Aletaha D, Smolen JS. The rheumatoid arthritis patient in the clinic: comparing more than 1,300 consecutive DMARD courses. Rheumatology (Oxford) 2002;41:1367-74.
25. Yamanaka H, Inoue E, Singh G, Tanaka E, Nakajima A, Taniguchi A, et al. Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan. Mod Rheumatol 2007;17:283-9.
26. Berard A, Solomon DH, Avorn J. Patterns of drug use in rheumatoid arthritis. J Rheumatol 2000;27:1648-55.
27. Edwards CJ, Arden NK, Fisher D, Saperia JC, Reading I, Van Staa TP, et al. The changing use of disease-modifying anti-rheumatic drugs in individuals with rheumatoid arthritis from the United Kingdom General Practice Research Database. Rheumatology (Oxford) 2005;44:1394-8.
28. Albers JM, Paimela L, Kurki P, Eberhardt KB, Emery P, van 't Hof MA, et al. Treatment strategy, disease activity, and outcome in four cohorts of patients with early rheumatoid arthritis. Ann Rheum Dis 2001;60:453-8.
29. Sokka T, Kautiainen H, Toloza S, Mäkinen H, Verstappen SM, Lund Hetland M, et al. QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Ann Rheum Dis 2007;66:1491-6.
30. Luukkainen R, Kajander A, Isomäki H. Effect of gold on progression of erosions in rheumatoid arthritis. Better results with early treatment. Scand J Rheumatol 1977;6:189-92.
31. Möttönen T, Hannonen P, Korpela M, Nissilä M, Kautiainen H, Ilonen J, et al. Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. Arthritis Rheum 2002;46:894-8.
32. Korpela M, Laasonen L, Hannonen P, Kautiainen H, Leirisalo-Repo M, Hakala M, et al. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. Arthritis Rheum 2004;50:2072-81.
33. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
34. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. Arthritis Rheum 2006;55:864-72.
35. van Dongen H, van Aken J, Lard LR, Visser K, Ronday HK, Hulsmans HM, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007;56:1424-32.
36. Finckh A. Early inflammatory arthritis versus rheumatoid arthritis. Curr Opin Rheumatol 2009;21:118-23.

Work Disability Caused by Early Rheumatoid Arthritis is Declining. Results from a Nationwide Finnish Register in 2000-2008

Vappu Rantalaiho[1], Hannu Kautiainen[2,3], Salme Järvenpää[4], Lauri Virta[5], Timo Pohjolainen[6], Markku Korpela[1], Timo Möttönen[7] and Kari Puolakka[8]

[1]Tampere University Hospital, Tampere, Finland; [2]Kuopio University Hospital, Kuopio, Finland; [3]Jyväskylä Central Hospital, Jyväskylä, Finland; [4]Medcare Foundation, Äänekoski, Finland, [5]Social Insurance Institution, Turku, Finland; [6]Orton Foundation, Helsinki, Finland; [7]University of Turku and Turku University Hospital, Turku, Finland; [8]Lappeenranta Central Hospital, Lappeenranta, Finland

Corresponding author: Vappu Rantalaiho, MD, Department of Internal Medicine, Centre for Rheumatic Diseases, Tampere University Hospital, PO BOX 2000, FI-33521 Tampere, FINLAND. Email: vappu.rantalaiho@pshp.fi. Telephone: +358 3 31165669, Fax + 358 3 311 64369.

Keywords: rheumatoid arthritis, disability leave

Word count: 2994 words

Abstract

Objectives. To study whether the work disability (WD) rates in early rheumatoid arthritis (RA) have changed in Finland, where the treatment of RA has long been active, but has, during this millennium, further intensified.

Methods. From a nationwide register maintained by The Finnish Social Insurance Institution (SII) we identified all incident, not-retired, working aged (18-64y) RA patients 1.1.2000-31.12.2007. Patient cohorts were analyzed in 2-year time periods (2000-01, 2002-03, 2004-05, 2006-07) and initial disease modifying antirheumatic drugs (DMARDs) were elucidated from the drug purchase register. The incidence of continuous work disability (WD) in the RA cohorts, as well as in the entire Finnish population up to 31.12.2008 was clarified.

Results. A total of 7 831 (71% female, 61% RF-positive) patients were identified. Throughout the follow-up, the use of methotrexate and combination-DMARDs increased as the initial treatment of early RA. During the first 2 years the incidence of RA related continuous WD was 8.9%, 9.4%, 7.2%, and 4.8% in the year cohorts, respectively, ($p < 0.001$ for linearity). Compared to the entire Finnish population, the age and sex stratified standardized incidence ratio of WD pension due to any cause was 3.69, 3.34, 2.77, and 2.80, in the year cohorts, respectively ($p<0.001$ for linearity).

Conclusions. During the present millennium, the frequency of continuous WD in early RA has declined in Finland. The present data allows no explanatory analysis, but at the same time increasingly active treatment strategies have been introduced.

Introduction

In clinical studies, the actively treated rheumatoid arthritis (RA) patients have had lower disease activity, more frequent remissions, and less radiographic progression than the conservatively treated ones.[1-5] These findings have led to specific treatment recommendations, and clinical practice appears to have changed accordingly.[6, 7]

Work disability (WD) is one of the hard outcomes of RA. Depending on study populations and on national differences in social security systems, 20-40% of the previously employed RA patients had become permanently work disabled within 2 years after the diagnosis and 40-80% 5-20 years after the diagnosis.[8] Some studies have shown that early remissions predict better maintenance of working capacity,[9] but how these study results translate into real life, is not evident. Biologic agents have shown promising results on clinical outcomes and their use has significantly increased during this millennium, but thus far their effect on the maintenance of RA patients' working capacity is ambiguous.[10-14]

Furthermore, there is a great national variance between the rates of permanent WD; in some countries RA patients with low disease activity become work disabled, while in others patients with severe disease activity continue working.[15, 16] Therefore the most reliable research method for trends in WD is to study them longitudinally in a same setting.

We have previously shown that in Finland the treatment of early RA has been active, and has recently further intensified.[7] In this study we wanted to elucidate whether this modern era has brought any changes in the trends in RA related WD in Finland.

Methods

Finland has a general sickness insurance covering the entire population, and all permanent residents are issued a personal health insurance. The Social Insurance Institution (SII) grants the patients with chronic inflammatory rheumatic disorders a special reimbursement of 72% for

antirheumatic drugs, and practically every Finnish patient with antirheumatic medications receives it. All medicine reimbursement decisions are gathered in a nationwide register maintained by the SII. Furthermore, the SII maintains a prescription register on the drugs purchased from pharmacies and reimbursed according to special rate.[7]

If Finnish residents aged 16-67 years become unable to perform their regular or corresponding jobs, they are entitled to a sickness allowance as a compensation for lost income. All 16-64 year-old persons who have lived in Finland for at least 3 years and who have an illness, injury or defect that prevents them from earning a reasonable living, stated by a doctor's certificate, can, after 150 working days of WD, and must, after 300 days of WD, apply either for a temporary rehabilitation allowance or a permanent disability pension. Permanent disability pensions are usually antedated by rehabilitation allowances of varying durations, and granted, at the earliest, after one year's WD, for persons over 60 years on somewhat easier terms. The SII and the Finnish Centre for Pensions maintain a register on sick leaves, rehabilitation allowances and permanent disability pension.

Patient cohort. From the nationwide register maintained by the SII we collected data of 18-64 year-old patients who were available for workforce when they, for the first time in their life, had been granted a special reimbursement of medications for rheumatoid factor (RF) positive (ICD-10 diagnosis M05) or RF-negative RA (M06) 1.1.2000-31.12.2007. The data included sex, birth date, and the date of reimbursement decision (index day, equalling RA diagnosis). No other clinical data were available. According to the index day, we analysed the patient data in 2-year cohorts (2000-01, 2002-03, 2004-05, 2006-07).

For these cohorts, from the registers of the SII and of the Finnish Centre for Pensions, we collected data of annual WD days, in 365 day cycles from the index date, including all periods of sickness allowance, temporary rehabilitation allowance, partial disability pensions (the number of the days divided by 2), and of permanent disability pension from one year before the index day up to the end of follow-up, 31.12.2008. However, sick leaves $\leq$10 days could not be assessed, as they

are not compensated by the SII. The annual WD days per patient years for any reason were counted. In this analysis also the patients already on partial pensions on index date were included.

During the same period the incidence of continuous WD was assessed by elucidating all permanent disability pensions and long-term rehabilitation allowances still continuing at the end of our follow-up, including continuous WD for any reason and that exclusively due to RA. The follow-up of the patients ended when they retired because of other reasons than RA, became 65 years old, or died, whichever the first. From the same institutes we received the incidence data of WD pensions of all 18-64 year-old Finnish citizens.

Further, from the reimbursement drug register, we gathered data on the drugs purchased by these patient cohorts from 31 days before to 91 days after the index day and investigated the early drug treatment strategies: no DMARD, any single DMARD, single methotrexate (MTX), any combination of DMARDs, or combination of DMARDs including MTX. The commencement of adalimumab or etanercept any time throughout the follow-up was elucidated. The intravenous drugs are given and paid by hospitals and outpatient clinics and not registered by the SII. Consequently, our study does not include infliximab or other infusion-based biologic therapies.

Ethical considerations. There was no legal requirement for approval by an ethics committee, since only unidentifiable register data were used and the patients were not contacted.

Statistical methods. Results are expressed as means with standard deviation (SD) and as medians with interquartile range (IQR). Statistical significance for hypotheses of linearity was evaluated by analysis of variance (ANOVA) or Cochran-Armitage test. Incidence of RA for each 2-year cohort with 95% confidence intervals (CIs) was calculated assuming a Poisson distribution using the 18-64 year old Finnish population (from Statistics Finland) as reference. The 95% CIs for annual WD days were obtained by bias-corrected bootstrapping and the linearity across year-cohorts was tested by bootstrap type analysis of covariance with an appropriate contrast. The cumulative incidence of continuous WD was estimated and illustrated by

Kaplan-Meier method. In order to adjust for confounding factors, the differences between the groups and the hypothesis of linearity were tested by using Cox's regression models with a contrast, when appropriate. Cox's multivariate regression model was also used to analyse factors associated to continuous WD. The patients with RA and the population at risk were stratified by gender, age (in 5 year categories), and calendar years, and incidence rates with 95% CIs were calculated. The ratio between observed and expected numbers, Standardized Incidence Ratio (SIR), was calculated with 95% CIs, assuming a Poisson distribution; significance for hypotheses of linearity was evaluated by Poisson regression models.

Results

We identified a total of 7831 (71% female, 61% RF-positive) working-aged (18-64 years) RA patients who, at the index date were available to work force full-time. Further, a cohort of 137 patients, already part-time retired at the index date, was included in the analysis of mean annual WD days. The demographic data is presented in Table 1. During the follow-up, the use of single-DMARD treatment during the first 3 months decreased, while that of combination-DMARDs increased. The use of MTX, either alone or in combinations, increased. The admission of adalimumab or etanercept for patients remained rare (Table 1).

Table 1. Demographic data and initial treatment strategies of the 7831 patients with a recent diagnosis of RA, available to workforce at baseline

Variable	Year cohort				
	2000-01 (N = 1998) N (%)	2002-2003 (N = 2043) N (%)	2004-05 (N = 1871) N (%)	2006-07 (N = 1919) N (%)	*p* for linearity
Female (%)	1422 (71)	1462 (72)	1291 (69)	1377 (72)	0.86
Age on index day, mean (SD)	45 (11)	46 (11)	47 (10)	46 (11)	<0.001
Rheumatoid factor present (%)	1135 (57)	1235 (60)	1161 (62)	1242 (65)	<0.001
Incidence of RA in the 18-64 year old population /100 000 per year (95% CI)	39 (37 to 40)	39 (38 to 41)	36 (35 to 38)	36 (35 to 38)	<0.001*
Initial treatment (≤ 3 months)					
No DMARDs	149 (7)	171 (8)	145 (8)	113 (6)	0.045
Any single DMARD	1072 (53)	1004 (49)	750 (40)	708 (36)	<0.001
Single MTX	166 (8)	196 (10)	243 (13)	295 (15)	
Any combination DMARDs	781 (39)	877 (43)	989 (53)	1105 (58)	<0.001
Combination including MTX	502 (25)	651 (32)	801 (43)	925 (48)	
Adalimumab or etanercept initiated at any time while available to workforce	79 (4)	84 (4)	85 (5)	29 (2)	NA

* age and sex adjusted

One year preceding the index date, the median (IQR) duration of >10 days WD periods was 0 (0 , 4) days per year in all cohorts. During the first year after index date, the mean number of annual WD days per patient years was similar in all year cohorts, 45-50 days per year. It decreased during the second year, increasing steadily thereafter (Figure 1). The mean number of annual WD days per patient years during the second year decreased along the year cohorts ($p = 0.002$ for linearity, adjusted for age, sex and RF). When the data of all cohorts during the first two years were analysed together, the number of the mean annual WD days per patient years was 53 in men, and 37 in women [mean ratio between men and women 1.42 (95% CI 1.28 to 1.54)], while 45.6% (95% CI

43.6 to 47.6%) of the men and 48.2% (95% CI 46.9 to 49.5%) of the women had no registered WD days during the first 2 years after the RA diagnosis.

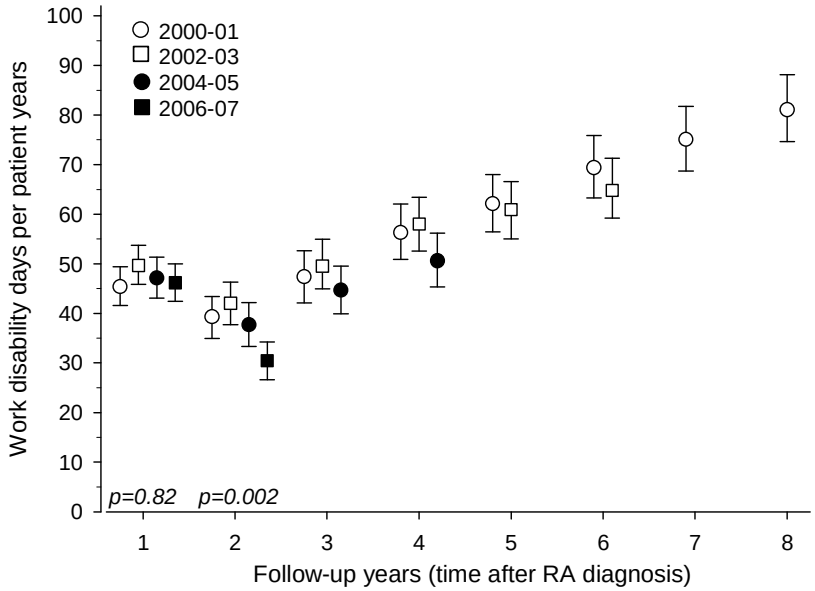

Figure 1. Mean annual WD days due to any cause per patient years in the early RA cohorts. The age and sex adjusted p-values show the statistical significance between the groups at years 1 and 2, during which all groups are followed up.

The median (IQR) follow-up time was 4.0 (2.2 , 6.3) years. By 8 years 14.5% (95% CI: 13.5 to 15.5) patients of the total patient population had retired due to RA. In women the cumulative incidence of RA dependent continuous WD was 12.6% (95% CI: 11.5-13.7) and in men 19.2% (95 % CI: 17.1 to 21.4) [age and RF adjusted HR = 0.68 (0.59 to 0.78), p <0.001] (Figure 2).

During the first 2 years after the diagnosis, the incidence of RA related continuous WD was 8.9% (95% CI 7.7 to 10.3), 9.4% (95% CI 8.2 to 10.8), 7.2% (95% CI 6.2 to 8.5), and 4.8% (95% CI 3.9 to 5.9) in the year cohorts 2000-01, 2002-03, 2004-05, and 2006-07, respectively (age, sex, and RF adjusted $p < 0.001$ for linearity). Figure 3 presents the Kaplan-Meier curves for continuous WD in different year cohorts during the 8-year follow-up.

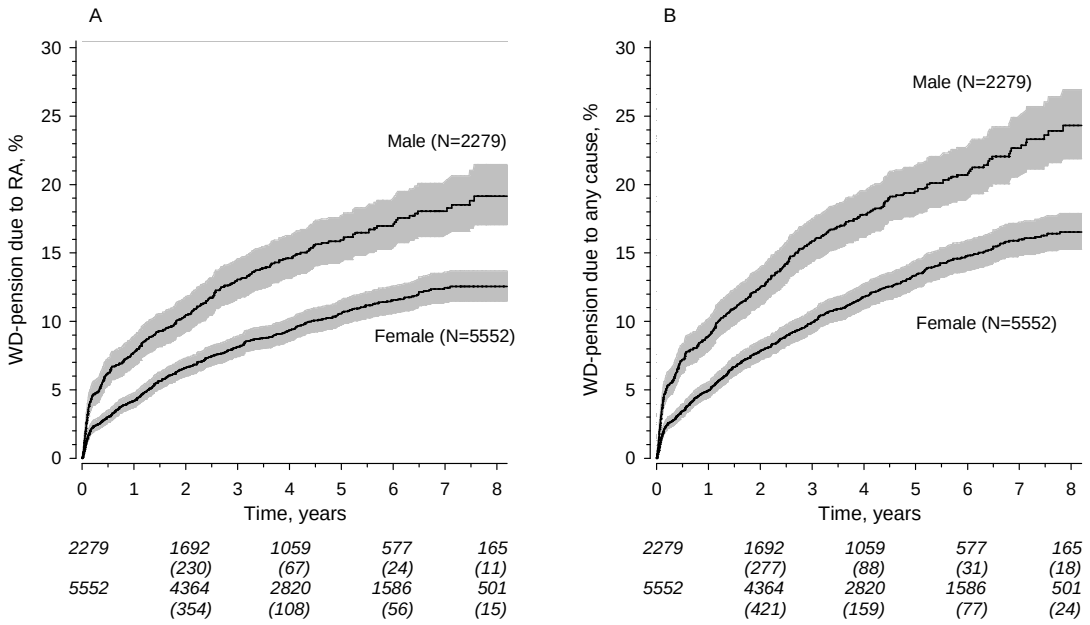

Figure 2. Kaplan-Meier curves with confidence intervals of the incidence of A) RA related continuous WD, and B) all-cause continuous WD in the male and the female patients after the diagnosis of RA. Under the x-axis are shown the numbers of male and female patients at risk at 0, 2, 4, 6, and 8 years on whom the estimates are based, and, in parenthesis, the numbers of events during the preceding period.

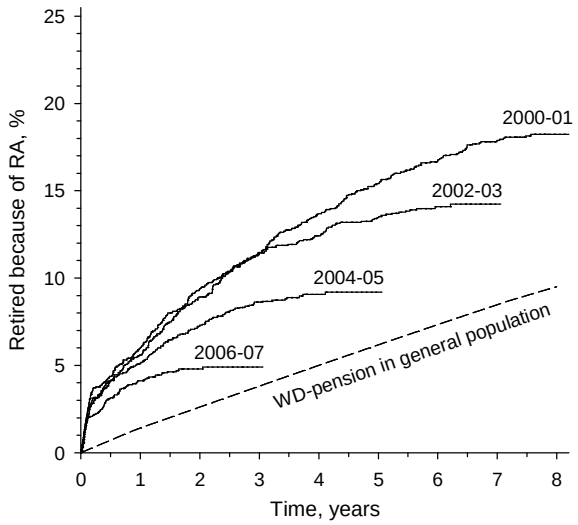

Figure 3. Kaplan-Meier curves of the incidence of continuous WD due to RA in different early RA patient cohorts. The dotted line describes the estimated cumulative incidence of WD pension due to any cause in general population.

In a Cox multivariate analysis for the total follow-up time, the year cohort, age, and sex were related to continuous WD (Table 2). In the same model, when single non-MTX DMARDS as an initial treatment was used as reference, all other active treatment strategies (but not no-DMARDs) significantly increased the risk of continuous WD. However, adalimumab and etanercept appeared to protect the patients from continuous WD (Table 2). Nevertheless, their use was rare, during the follow-up these TNF-inhibitors were prescribed to 277 patients [70% female, mean (SD) age on index day 41 (12)] (Table 1), and were started on average 2.6 (SD 1.8) years after the index day.

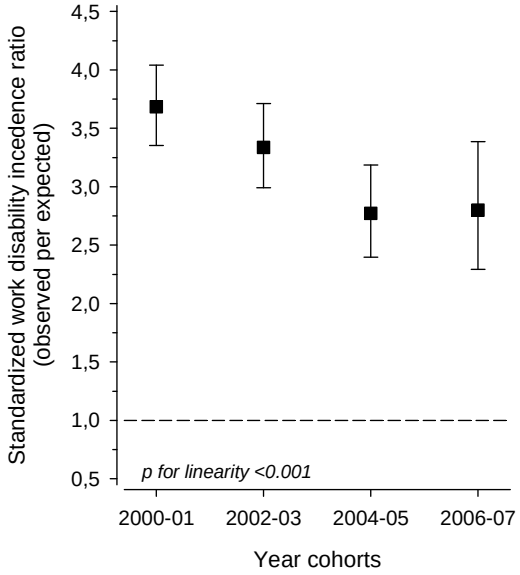

Figure 4. The standardised incidence ratio (SIR) for a premature disability pension due to any cause in the Finnish early RA patients compared to the general Finnish population. The Finnish legislation was reformed in 2004; prioritizing vocational rehabilitation over WD pensions.

Table 2. Cox multivariate regression analysis on factors predicting continuous, RA related WD in patients with a recent diagnosis of RA

	HR (95% CI)	*p*-value
Age	1.08 (1.07 to 1.09)	<0.001
Male	1.50 (1.31 to 1.72)	<0.001
RF present	1.12 (0.97 to 1.30)	0.11
Year cohort		<0.001*
2000-01	1 (reference)	
2002-03	0.79 (0.67 to 0.93)	
2004-05	0.51 (0.42 to 0.61)	
2006-07	0.35 (0.27 to 0.44)	
Medication (first 3 months)		<0.001
Single other	1 (reference)	
Single MTX	1.33 (1.05 to 1.69)	
Combi other	1.28 (1.02 to 1.62)	
Combi including MTX	1.52 (1.29 to 1.79)	
None	1.17 (0.89 to 1.54)	
Adalimumab or etanercept initiated at any time while available to workforce	0.61 (0.39 to 0.97)	0.036
The number of WD days the year before the index day, corresponding to one month's change	1.12 (1.06 to 1.18)	<0.001

* *p* for linearity

In the whole working aged Finnish population the incidence of preterm WD pension for any reason remained stable; it was 0.7% in 2000 and 0.8% in 2008. Compared to the Finnish population, the age and sex stratified incidence ratio (SIR) for WD pension in our early RA population was 3.16 (95% CI 2.97 to 3.35) and it declined along the year cohorts (Figure 4).

Discussion

This study shows that in Finland the frequency of continuous WD in early RA is declining, while the incidence of all disability pensions in the Finnish population has remained stable. This favourable development has occurred in parallel with increasingly active treatment strategies used for early RA, even though we failed to confirm a direct protective relationship between traditional DMARD treatments and WD.

The first year after the diagnosis of RA the majority of WD days are due to temporary sick leaves, thereafter mainly to permanent disability pensions, as shown by the FIN-RACo study.[17] The rates of permanent WD in earlier cohorts of RA patients have been around 20 % after 2 years, and 50 % after 5 years of RA.[8] Especially in European studies the WD has occurred quite early after the diagnosis of RA,[18, 19] whereas in the US, presumably due to differences in the sickness benefit systems, permanent WD has increased only later in the disease course.[20] Compared to earlier European and Scandinavian, even earlier Finnish reports,[21-25] the novel Finnish WD rates in early RA appear clearly lower, with their incidence further decreasing. A recent large Swedish study found a similar trend of decreasing number of annual WD days in the latest early RA cohort compared to earlier cohorts.[26] However, the annual WD days in these Swedish cohorts were 2-4 times higher than in the current Finnish cohorts, and the proportion of patients not utilizing sick leave was lower than in our cohorts.

There are some possible explanations for the declining trend in RA depended WD. Firstly, legislative changes could affect the permanent WD pension rates, and indeed, in Finland, the legislation was reformed in 2004; prioritizing vocational rehabilitation over WD pension, and transferring the responsibility of organising it to the pension providers. While it is possible that this has affected the WD pension rates in RA patients, the rate of WD pensions in the general population remained at a similar level throughout the follow-up.

The earlier data comparing the incidence of permanent WD between early RA patients and general population are sparse. Two studies from The Netherlands found a 4-7-fold risk for WD in early RA compared to general population,[19, 27] and an UK study even a 32-fold risk.[28] Compared to them, the 3-fold risk caused by early RA found in this study is remarkably lower but presents still a considerable menace, giving an informative estimate for the patients and for the authorities of the current threat that RA causes to the patients' working ability.

The second possible explanation for the decline of continuous WD in early RA is the contemporary change in treatment strategies, aiming at early diagnosis and treatment, targeting remission or low disease activity. We too found a shift towards more active treatment strategies in early RA during our follow-up.[7] Still, undoubtedly due to a channelling bias, the patients with the mildest initial treatment, i.e. single non-MTX DMARD had a lower risk of WD than the patients initially treated more actively. However, it is evident that in the continuum of clinical disease activity in early RA, the patients with a mild RA, and therefore the best prognosis to start with, are the ones prescribed the mildest treatments. And the patients receiving more aggressive treatments are the ones with an active disease and thus an unfavourable consequent working ability scenario. Most probably, still, had any of these patients been treated with less effective strategies, their WD rates would be much higher.

Regardless of the channelling bias discussed above, TNF-inhibitors (adalimumab and etanercept) protected the patients' working ability. Nevertheless, their use was uncommon, and they were started firstly after a few years from the diagnosis, thus the use of biologics cannot explain but a very small part of the total decline of RA disability pensions. Our data on biologics is unfortunately limited, as we have no data on hospital-based medications such as infliximab, which are not reimbursed by the SII but funded by hospitals. Infliximab was the first TNF-inhibitor to become available in Finland in 1999. Etanercept became available in 2002, and adalimumab in 2003, and the other biologics only after the end of our study period. After their introduction, the SII-

reimbursed etanercept and adalimumab often displaced infliximab as the first biologic for financial reasons. All of the biologics were first reserved for RA patients with treatment-resistant and therefore often longstanding disease and their use in early RA was exceptional.[29] Therefore, more evidence is needed about the role of early biologic treatment on maintaining working ability.

The third potential explanation for the decline in disability pensions are both the patients' and the physicians' altered attitudes towards the prognosis of RA; with new possibilities to treat RA towards better outcomes permanent inability to work has ceased to be a self-evident consequence of RA. Furthermore, the authorities giving their expert opinion on whether a patient is qualified for a disability pension may have adopted a similar change in attitude.

The great strength of our study is that it is unbiased, including all Finnish early RA patients, not only particular, in various ways selected, populations. Moreover, we have highly reliable and extensive register data on WD as well as on RA medications. Also the comparison to general population is reliable, as all Finnish citizens available to work force are included in the control material.

A limitation of our register-based study is the patient inclusion on grounds of the drug reimbursement decision, which, however, practically all Finnish RA patients receive.[7] Further, the incidence of RA in the present population[30] is not lower than in earlier reports from Finland[31] or from other countries,[32] indicating comprehensive patient inclusion.

Other limitations of our study are that we have no data on short (<10 days) sick leaves, since they are not registered by the SII, making our results an underestimate, and more importantly, the lack of clinical and radiographic data and on details of employment and schooling of the patients, which forbids us from analyzing the patient dependent factors behind the observed trend in WD pensions. However, ample evidence has shown that amongst the main patient depending factors predicting WD are severe and long-standing RA, reduced functional ability, physically demanding work and older age.[8] Of these, we confirmed higher age to be a significant risk factor for

premature WD in early RA. Interestingly, we also found male patients to have a clearly higher risk of RA related WD than females. One earlier study showed a slightly increased risk for arthritis related WD in males,[33] some have found an increased risk in females;[16, 26, 34] and others no gender-association.[18, 19, 35, 36] Further, different risk factors predispose males and females to WD.[37] Nonetheless, comparing our results with those of others is difficult as we lack the clinical and socioeconomic data, and as some studies include patients with self-announced arthritis of any type.[33, 34] Also, defining WD according to the patient's own announcement of not being employed might produce nebulous results, [35] especially in countries where women are not as active a component of workforce as in Finland, where the participation to workforce is similar in working aged males and females; 70 % and 71 % respectively in 2008 according to Statistics Finland. Thus, higher engagement to housekeeping and lesser to paid employment does not explain the lower risk for WD in females. Nevertheless, male workers being possibly more often occupied in manual labour than female workers could partially explain our finding.

To conclude, our results demonstrate that it is possible to decrease or to postpone long-term WD in patients with early RA. This development has occurred in parallel with increasingly active treatments with conventional DMARDs, possibly altered attitudes towards the prognosis of RA, and legislative changes emphasizing vocational rehabilitation. The use of TNF-inhibitors contributes to preserving the patients' working ability, but their use explains but a minor part of this favourable outcome, at least in Finland.

Licence for Publication

such use and exploit all subsidiary rights, as set out in our licence (http://group.bmj.com/products/journals/instructions-for-authors/licence-forms).

Competing Interest: None declared.

References

1 Möttönen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353:1568-73.

2 Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263-9.

3 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med 2007;146:406-15.

4 Rantalaiho V, Korpela M, Hannonen P, et al. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: The eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. Arthritis Rheum 2009;60:1222-31.

5 Rantalaiho V, Korpela M, Laasonen L, et al. Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. Arthritis Res Ther 2010;12:R122.

6 Ziegler S, Huscher D, Karberg K, et al. Trends in treatment and outcomes of rheumatoid arthritis in Germany 1997-2007: results from the National Database of the German Collaborative Arthritis Centres. Ann Rheum Dis 2010;69:1803-8.

7 Rantalaiho V, Kautiainen H, Virta L, et al. Trends in treatment strategies and the usage of different disease-modifying anti-rheumatic drugs in early rheumatoid arthritis in Finland. Results from a nationwide register in 2000-2007. Scand J Rheumatol 2010;40:16-21.
8 Verstappen SM, Bijlsma JW, Verkleij H, et al. Overview of work disability in rheumatoid arthritis patients as observed in cross-sectional and longitudinal surveys. Arthritis Rheum 2004;51:488-97.
9 Puolakka K, Kautiainen H, Möttönen T, et al. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. Arthritis Rheum 2005;52:36-41.
10 Smolen JS, Han C, van der Heijde D, et al. Infliximab treatment maintains employability in patients with early rheumatoid arthritis. Arthritis Rheum 2006;54:716-22.
11 Allaire S, Wolfe F, Niu J, et al. Evaluation of the effect of anti-tumor necrosis factor agent use on rheumatoid arthritis work disability: the jury is still out. Arthritis Rheum 2008;59:1082-9.
12 Verstappen SM, Watson KD, Lunt M, et al. Working status in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2010;49:1570-7.
13 Neovius M, Simard JF, Klareskog L, et al. Sick leave and disability pension before and after initiation of antirheumatic therapies in clinical practice. Ann Rheum Dis 2011;70:1407-14.
14 Augustsson J, Neovius M, Cullinane-Carli C, et al. Patients with rheumatoid arthritis treated with tumour necrosis factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry). Ann Rheum Dis 2010;69:126-31.
15 Chung CP, Sokka T, Arbogast PG, et al. Work disability in early rheumatoid arthritis: higher rates but better clinical status in Finland compared with the US. Ann Rheum Dis 2006;65:1653-7.

16 Sokka T, Kautiainen H, Pincus T, et al. Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. Arthritis Res Ther 2010;12:R42.

17 Puolakka K, Kautiainen H, Pekurinen M, et al. Monetary value of lost productivity over a 5-year follow up in early rheumatoid arthritis estimated on the basis of official register data on patients' sickness absence and gross income: experience from the FIN-RACo Trial. Ann Rheum Dis 2005;65:899-904.

18 Doeglas D, Suurmeijer T, Krol B, et al. Work disability in early rheumatoid arthritis. Ann Rheum Dis 1995;54:455-60.

19 Albers JM, Kuper HH, van Riel PL, et al. Socio-economic consequences of rheumatoid arthritis in the first years of the disease. Rheumatology (Oxford) 1999;38:423-30.

20 Wolfe F, Hawley DJ. The longterm outcomes of rheumatoid arthritis: Work disability: a prospective 18 year study of 823 patients. J Rheumatol 1998;25:2108-17.

21 Mäkisara GL, Mäkisara P. Prognosis of functional capacity and work capacity in rheumatoid arthritis. Clin Rheumatol 1982;1:117-25.

22 Kaarela K, Lehtinen K, Luukkainen R. Work capacity of patients with inflammatory joint diseases. An eight-year follow-up study. Scand J Rheumatol 1987;16:403-6.

23 Jäntti J, Aho K, Kaarela K, et al. Work disability in an inception cohort of patients with seropositive rheumatoid arthritis: a 20 year study. Rheumatology (Oxford) 1999;38:1138-41.

24 Sokka T, Kautiainen H, Mottonen T, et al. Work disability in rheumatoid arthritis 10 years after the diagnosis. J Rheumatol 1999;26:1681-5.

25 Puolakka K, Kautiainen H, Möttönen T, et al. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. Arthritis Rheum 2004;50:55-62.

26 Neovius M, Simard JF, Askling J. How large are the productivity losses in contemporary patients with RA, and how soon in relation to diagnosis do they develop? Ann Rheum Dis 2011;70:1010-5.
27 van Jaarsveld CH, Jacobs JW, Schrijvers AJ, et al. Effects of rheumatoid arthritis on employment and social participation during the first years of disease in The Netherlands. Br J Rheumatol 1998;37:848-53.
28 Barrett EM, Scott DG, Wiles NJ, et al. The impact of rheumatoid arthritis on employment status in the early years of disease: a UK community-based study. Rheumatology (Oxford) 2000;39:1403-9.
29 Virkki L, Aaltonen K, Nordstrom D. [Biological therapy in rheumatoid arthritis based on ten years of registry surveillance in Finland]. Duodecim 2010;126:1487-95.
30 Puolakka K, Kautiainen H, Pohjolainen T, et al. Rheumatoid arthritis (RA) remains a threat to work productivity: a nationwide register-based incidence study from Finland. Scand J Rheumatol 2010;39:436-8.
31 Kaipiainen-Seppänen O, Kautiainen H. Declining trend in the incidence of rheumatoid factor-positive rheumatoid arthritis in Finland 1980-2000. J Rheumatol 2006;33:2132-8.
32 Gabriel SE, Crowson CS, Kremers HM, et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. Arthritis Rheum 2003;48:54-8.
33 Badley EM, Wang PP. The contribution of arthritis and arthritis disability to nonparticipation in the labor force: a Canadian example. J Rheumatol 2001;28:1077-82.
34 Kaptein SA, Gignac MA, Badley EM. Differences in the workforce experiences of women and men with arthritis disability: a population health perspective. Arthritis Rheum 2009;61:605-13.
35 Allaire S, Wolfe F, Niu J, et al. Current risk factors for work disability associated with rheumatoid arthritis: recent data from a US national cohort. Arthritis Rheum 2009;61:321-8.

36 Puolakka K, Kautiainen H, Möttönen T, et al. Predictors of productivity loss in early rheumatoid arthritis: a 5 year follow up study. Ann Rheum Dis 2005;64:130-3.
37 De Roos AJ, Callahan LF. Differences by sex in correlates of work status in rheumatoid arthritis patients. Arthritis Care Res 1999;12:381-91.