TIINA LEVÄLAMPI

Anti-TNFα Therapy in the Treatment of Rheumatoid Arthritis, Spondyloarthropathies and Juvenile Idiopathic Arthritis

■

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the Auditorium of
Tampere School of Public Health, Medisiinarinkatu 3,
Tampere, on December 11th, 2009, at 12 o'clock.

UNIVERSITY OF TAMPERE

ACADEMIC DISSERTATION
University of Tampere, Medical School
Tampere University Hospital
Rheumatism Foundation Hospital, Heinola
Clinical Drug Research Graduate School
Finland

Supervised by
Professor Eeva Moilanen
University of Tampere
Finland
Docent Markku Korpela
University of Tampere
Finland

Reviewed by
Professor Risto Huupponen
University of Turku
Finland
Docent Anneli Savolainen
University of Tampere
Finland

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

Tel. +358 3 3551 6055
Fax +358 3 3551 7685
taju@uta.fi
www.uta.fi/taju
http://granum.uta.fi

Cover design by
Juha Siro

Acta Universitatis Tamperensis 1474
ISBN 978-951-44-7906-9 (print)
ISSN-L 1455-1616
ISSN 1455-1616

Acta Electronica Universitatis Tamperensis 909
ISBN 978-951-44-7907-6 (pdf)
ISSN 1456-954X
http://acta.uta.fi

Tampereen Yliopistopaino Oy – Juvenes Print
Tampere 2009

CONTENTS

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 In addition, some unpublished data are presented.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 Levälampi T, Honkanen V, Lahdenne P, Nieminen R, Hakala M, Moilanen E (2007): Effects of infliximab on cytokines, myeloperoxidase, and soluble adhesion molecules in patients with juvenile idiopathic arthritis. Scand J Rheumatol 36:189-193.

II Levälampi T, Korpela M, Vuolteenaho K, Moilanen E (2008): Infliximab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: adverse events and other reasons for discontinuation of treatment. Scand J Rheumatol 37:6-12.

III Levälampi T, Korpela M, Vuolteenaho K, Moilanen E (2008): Etanercept and adalimumab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: adverse events and other reasons leading to discontinuation of the treatment. Rheumatol Int 28:261-269.

IV Levälampi T, Korpela M, Vuolteenaho K, Moilanen E (2009): Infliximab treatment in patients with rheumatoid arthritis and spondyloarthropathies in one rheumatological centre; two years drug survival. (Rheumatol Int in press)

Abbreviations

ACR	The American College of Rheumatology
APC	antigen-presenting cells
AS	ankylosing spondylitis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
CD	Crohn's Disease
COX	cyclooxygenase
CRP	C-reactive protein
DAS	Disease Activity Score
DMARD	disease modifying antirheumatic drug
DNA	deoxyribonucleic acid
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GI	gastrointestinal
HLA	human leukocyte antigen(s)
HAQ	Health Assessment Questionnaire
IBD	inflammatory bowel disease
ICAM	intercellular adhesion molecule
IKK	inhibitor of NF-κB kinase
IL	interleukin
ILAR	International League of Associations for Rheumatology
JIA	juvenile idiopathic arthritis
MHC	major histocompatibility
MMP(s)	matrix metalloprotease(s)
MRI	magnetic resonance imaging
mTNFα	transmembrane TNFα
NF-κB	nuclear factor κB

NSAID	nonsteroidal anti-inflammatory drug
PsA	psoriathic arthritis
RA	rheumatoid arthritis
SE	shared epitope
SLE	systemic lupus erythematosus
SpA	spondyloarthropathy
TACE	TNFα-converting enzyme
TNFα	tumor necrosis factor alpha
TNFR	tumor necrosis factor receptor
TRAF	TNF receptor-associated factor
UC	ulcerative colitis
VAS	visual analogue scale

Abstract

Rheumatoid arthritis (RA) is a polyarticular inflammatory joint disease with a prevalence of about 1% in the adult population. The severity of the disease varies between mild self limiting illness to aggressive, drug resistant disease which causes joint destruction and deformity, and ultimately severe disability. Spondyloarthropathies (SpA) are a group of diseases composed of inflammatory conditions such as asymmetric oligoarthritis of the lower extremities. Prevalence of SpA is estimated to be around 1% in Europe. Juvenile idiopathic arthritis (JIA) represents a heterogenous group of chronic inflammatory conditions occurring in childhood or adolescence in which the cause of arthritis remains unknown. Prevalence of JIA varies between 7-400/100.000 children. Due to its heterogeneity, the drug treatment also varies between different subtypes of JIA.

In an inflamed joint, the synovium is converted into histologically differentiated pannus as a result of the influences of different inflammatory cells, cytokines and other mediators which also act together with matrix metalloproteases (MMPs) to inflict dysregulation of chondrocytes and degradation of articular cartilage. Tumor necrosis factor alpha (TNFα) and interleukin 1β (IL-1β) are key factors driving rheumatoid inflammation in the joint, eventually leading to erosions.

The American College of Rheumatology (ACR) criteria are often used to define the clinical response to the treatment in RA. ACR20, ACR50 and ACR70 response criteria represent clearly defined 20%, 50% and 70% improvements in the core set of criteria, respectively. The clinical response to the drug treatment in SpA can be assessed by using BASDAI (Bath Ankylosing Spondylitis Disease Activity Index). Treatment is regarded as ineffective if the reduction of BASDAI index is lower than 50% or less than 2 cm.

According to the national guidelines in Finland, the criterion for initiating anti-TNFα therapy in RA patients is that the patient is suffering from a severe and refractory disease despite active drug treatment. Anti-TNFα therapy is usually added on to one disease modifying antirheumatic drug (DMARD) or to the combination of two or more DMARDs. The drug treatment is actively adjusted to achieve clinical remission or at least an ACR50 response. In SpA patients, anti-TNFα therapy is indicated if the patient has active disease despite treatment with DMARDs, like sulfasalazine. Anti-TNFα therapy is adjusted to achieve clinical remission or at least 50% response as assessed by BASDAI.

The aim of the present study was to (1) investigate the effects of infliximab treatment on inflammatory mediator levels in patients with severe JIA, and (2) to study drug survival during anti-TNFα therapy in patients with DMARD resistant RA or SpA.

Blood samples were collected from eight JIA patients who responded favourably to infliximab treatment. Clinical effects were seen already after six weeks of treatment. Interleukin 6 (IL-6) concentrations decreased to about half

and myeloperoxidase (MPO) levels by about 35% during the 12 weeks' treatment period. In addition, the levels of soluble forms of adhesion molecules ICAM-1 and E-selectin became reduced in response to infliximab treatment. TNFα levels tended to increase while the levels of endogenous TNFα antagonists (soluble TNF receptors) were reduced in most of the patients during treatment.

In the second part of the study, drug survival in 104 infliximab-treated patients was evaluated after six, 12 and 24 months of treatment, and in 53 etanercept and 43 adalimumab-treated patients after 12 months. Drug survival in infliximab-treated RA and SpA patients after six, 12 and 24 months' follow-up was 71%, 53% and 40%, respectively. The reasons for discontinuations were remission (7% in six months / 8% in 12 months / 7% in 24 months), adverse event (13% / 16% / 24%) and lack of efficacy (8% / 16% / 22%). Infections and hypersensitivity reactions were the main adverse events requiring discontinuation of infliximab treatment, and also two cases of drug related leukopenia and one case of elevated aminotransferases were observed. After 12 months, the continuation rate was 74% in the etanercept and 60% in the adalimumab-treated patients. Eleven patients were regarded as poor responders, seven (13%) in the etanercept group and four (9%) in the adalimumab group. Adverse events (mainly infections and injection reactions) caused six (11%) discontinuations in etanercept-treated group and 11 (26%) discontinuations in adalimumab group. Etanercept was discontinued due to some other adverse event in two patients, in one patient due to adenocarcinoma of the ovary and in one patient due to drug related leukopenia. One patient treated with adalimumab developed the clinical and immunological features of systemic lupus erythematosus (SLE).

In summary, treatment with a TNFα antagonist infliximab reduced the levels of inflammatory mediators IL-6, MPO and soluble ICAM-1 and E-selectin in conjunction with a good clinical response in patients with JIA. Drug survival in RA and SpA patients with one or more DMARDs in addition to infliximab, etanercept or adalimumab treatment was good and comparable to the results obtained in previous observational studies in patients with less-severe disease. The use of concomitant DMARDs or oral glucocorticoids could be diminished. The results support the clinical view that combination of DMARDs and TNFα antagonists is an effective and relatively safe treatment of severe and DMARD-refractory RA and SpA. In the future, specifying the pathogenetic mechanism of RA, SpA and JIA as well as finding more specific biomarkers will improve the drug development and assist to design the drug treatment to meet the needs of the individual patient.

Tiivistelmä

Nivelreuma (RA) on pitkäaikainen, useiden nivelten tulehduksellinen sairaus, jonka esiintyvyys väestössä on n. 1%. Taudin vaikeusaste vaihtelee lievästä taudinkuvasta aggressiiviseen ja vaikeaan niveliä tuhoavaan ja lääkkeille reagoimattomaan tautiin, joka voi johtaa potilaan toimintakyvyn vaikeaan alenemiseen.

Spondyloartropatiat (SpA) ovat ryhmä tulehduksellisia selkäsairauksia, joihin voi liittyä erilaisia ilmenemismuotoja, kuten alaraajoihin painottuvia niveltulehduksia. Tautiryhmän esiintyvyys väestössä on samaa luokkaa kuin nivelreuman esiintyvyys. Lastenreuma (JIA) puolestaan koostuu ryhmästä erilaisia lapsuus- tai nuoruusiässä alkavia tulehduksellisia sairauksia, joissa niveltulehduksen syy on epäselvä ja oireet kestävät vähintään kuusi viikkoa. Johtuen tautimuotojen erilaisuudesta, myös lääkehoito eroaa eri lastenreumamuotojen välillä. Lastenreuman esiintyvyys vaihtelee eri aineistoissa välillä 7-400/100.000 lasta.

Tulehtuneessa nivelessä nivelkalvo paksuntuu ja muodostaa ns. pannus-kudoksen ruston ja nivelkalvon rajalle. Tulehdussolujen ja nivelkalvon solujen tuottamat tulehdusvälittäjäaineet voimistavat niveltulehdusta ja johtavat kondrosyyttien toimintahäiriöön sekä yhdessä matriksin metalloproteinaasi (MMP)-entsyymien kanssa saavat aikaan nivelruston vaurioitumisen ja ohenemisen. Tuumorinekroositekijä α (TNFα) ja interleukiini 1β (IL-1β) ovat tärkeitä välittäjäaineita niveltulehduksessa ja rustovaurion kehittymisessä.

Lääkevasteen arviointia varten on kehitetty erilaisia arviointimenetelmiä, joista yksi käytetyimmistä on Amerikan reumatologiyhdistyksen ACR-paranemiskriteeri. ACR20, ACR50 ja ACR70 edustavat potilaan tilan arvioinnissa 20 %, 50 % tai 70 % paranemista lähtötilanteeseen verrattuna. Selkärankareumapotilailla käytetään vastaavanlaista tulehduksen vaikeusasteen arviointimenetelmää BASDAI (Bath Ankylosing Spondylitis Disease Activity Index). Hoito luokitellaan teholtaan riittämättömäksi, jos muutos BASDAI-indeksissä on pienempi kuin 50% tai vähemmän kuin 2 cm asteikolla 1-10 cm.

Suomessa nivelreuman Käypä hoito -suosituksen mukaan biologinen lääkehoito aloitetaan, jos potilas kärsii aktiivisesta taudista yhdistelmälääkehoidosta huolimatta. Biologinen lääke lisätään usein potilaan aikaisempaan yhden reumalääkkeen hoitoon tai useamman reumalääkkeen yhdistelmähoitoon. Lääkehoitoa muutetaan aktiivisesti, jotta saavutetaan remissio tai ainakin 50 %:n paraneminen oireissa (ACR50-paranemiskriteeri).

Tutkimuksen tarkoitus oli (1) tutkia infliksimabi-hoidon vaikutusta tulehduksellisiin välittäjäaineisiin vaikeaa lapsireumaa sairastavilla potilailla, joilla saavutettiin hyvä kliininen vaste tällä hoidolla sekä (2) selvittää biologisen lääkehoidon toteutumista nivelreuma- ja spondyloartropatiapotilailla.

Tutkimusnäytteet kerättiin lapsireumapotilailta, jotka saivat infliksimabi-hoitoa. Potilaat hyötyivät lääkityksestä ja kliiniset vaikutukset olivat nähtävissä jo kuuden viikon kuluttua hoidon aloittamisesta. Seerumin interleukiini 6 (IL-6) pitoisuudet laskivat puoleen ja myeloperoksidaasi-entsyymin (MPO) tasot laskivat noin 35% 12 viikon hoidon aikana. Lisäksi liukoisten adheesiomolekyylien (sICAM-1 ja sE-selektiini) pitoisuudet laskivat infliksimabi-hoidon aikana. Seerumin TNFα-tasot nousivat, mutta endogeenisten TNFα:n reseptorisalpaajien (liukoiset TNF reseptorit sTNFR1 ja sTNFR2) tasot laskivat suurimmalla osalla potilaista.

Tutkimuksen toisessa osassa lääkehoidon toteutuminen infliksimabi-hoitoa saaneilla RA ja SpA potilailla arvioitiin kuuden, 12 ja 24 kuukauden sekä etanersepti- ja adalimumabi-hoitoa saaneilla potilailla 12 kuukauden kohdalla. Lääkehoito jatkui onnistuneesti infliksimabi-hoitoa saaneilla potilailla kuuden, 12 ja 24 kuukauden hoidon jälkeen 71%, 53% ja 40%:lla potilaista. Syyt hoidon keskeytykseen olivat remissio (7%:lla kuuden, 8%:lla 12 ja 7%:lla 24 kuukauden kohdalla), haittavaikutus (13% / 16% / 24%) sekä hoidon tehottomuus (8% / 16% / 22%). Yleisimmät lääkehoidon keskeytykseen johtaneet haittavaikutukset olivat yliherkkyysreaktiot ja infektiot. Aineistossa todettiin myös kaksi lääkehoidon aikana kehittynyttä ja todennäköisesti siihen liittyvää leukopenia-tapausta sekä yhdellä potilaalla maksaentsyymiarvon nousu. Kahdentoista kuukauden seurannan jälkeen hoitoa jatkoi 74% potilaista etanersepti-ryhmässä ja 60% adalimumabi-ryhmässä. Etanersepti- ja adalimumabi-hoidon lopettaneista potilaista 11 ei reagoinut lääkehoitoon riittävän hyvin, seitsemän (13%) etanersepti-ryhmässä ja neljä (9%) adalimumabi-ryhmässä. Haittavaikutukset (pääasiassa infektiot ja yliherkkyysreaktiot) aiheuttivat kuusi (11%) lääkehoidon lopettamista etanersepti-ryhmässä sekä 11 (26%) adalimumabi-ryhmässä. Etanerseptihoidon aikana yhdellä potilaalla todettiin munasarjan adenokarsinooma ja toisella potilaalla leukopenia. Yhdelle adalimumabilla hoidetulle potilaalle kehittyi reaktio, joka kliiniseltä ja immunologiselta piirteiltään muistutti systeemistä lupus erytematosusta (SLE).

Yhteenvetona voidaan todeta, että TNFα-salpaajat ovat hyvin siedettyjä ja turvallisia lääkkeitä nivelreumaa ja spondyloartropatiaa sairastavilla potilailla. Lastenreumaa sairastavilla potilailla hoito TNFα-salpaajalla alensi tulehdusvälittäjäaineiden IL-6:n ja MPO:n sekä liukoisten ICAM-1:n ja E-selektiinin pitoisuuksia hyvän kliinisen vasteen myötä. Tutkimuksen toisessa osassa tutkittiin TNFα-salpaajahoidon onnistumista nivelreuma- ja spondyloartropatia-potilailla, joilla oli vakava lääkkeille resistentti reumasairaus. Potilaat hyötyivät hoidosta ja tulokset ovat samansuuntaisia kuin kansainvälisissä tutkimuksissa, joissa potilaiden reumasairauden vaikeusaste on useimmiten lievempi. Kuitenkin tässä tutkimuksessa oli nähtävissä tehon hiipumista ajan myötä varsinkin infliksimabi-hoitoa saaneilla potilailla. Tulokset tukevat kliinistä näkemystä perinteisen reumalääkityksen ja TNFα-salpaajan yhdistelmähoidon tehosta ja suhteellisesta turvallisuudesta vaikean ja lääkeresistentin nivelreuma- ja spondyloartropatian hoidossa. Tulevaisuudessa reumasairauksien patogeneettinen mekanismi todennäköisesti tarkentuu ja sitä kautta mahdollisten biomerkkiaineiden löytyminen voi edelleen parantaa ja tarkentaa lääkekehitystä sekä ohjata yksilölliseen hoidon valintaan.

Introduction

Tumor necrosis factor α (TNFα) is an important cytokine involved in systemic inflammation. TNFα has a primary role in the activation of immune cells and in the regulation of production of cytokines and other inflammatory factors. Dysregulation of inflammatory factors, in particular overproduction of TNFα, has been implicated in chronic inflammatory diseases, such as rheumatoid arthritis (RA) and spondyloarthropathies (SpA). The central role of TNFα in those diseases is supported by the fact that blocking a single cytokine i.e. TNFα with a TNFα antagonist, changes the levels of inflammatory mediators and confers a potent anti-inflammatory and antierosive effect in patients with RA and SpA (Feldmann et al. 1996, Feldmann and Maini 2001, Braun and Sieper 2007).

TNFα antagonists are novel anti-inflammatory and antierosive drugs which have been found to be effective and well-tolerated in the treatment RA, SpA and juvenile idiopathic arthritis (JIA). TNFα antagonists are molecules that bind to the cytokine TNFα and inhibit its biological activity. In the present study, three TNFα antagonists were investigated. *Infliximab* is a chimeric human and mouse monoclonal anti-TNFα antibody. *Etanercept* is a human TNFα receptor p75 fusion protein, and *adalimumab* is a humanized TNFα monoclonal antibody.

Traditional drug treatment of RA and SpA consists of non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (intra-articular and oral), and one or more disease modifying anti-rheumatic drugs (DMARDs). Despite active treatment with non-biological DMARDs, many patients do not respond adequately to the drug treatment, or the drug treatment causes unacceptable adverse events. According to the national guidelines (Rheumatoid arthritis: Current Care Guidelines 2009), anti-TNFα therapy needs to be added to combination DMARD therapy when patients continue to have active and refractory RA.

The aim of the present study was (1) to investigate inflammatory mediators during infliximab treatment in JIA patients and (2) to investigate drug survival

during infliximab, etanercept or adalimumab treatment in patients with RA and SpA.

Review of the literature

1 Rheumatoid arthritis

1.1 Epidemiology of rheumatoid arthritis

Rheumatoid arthritis (RA) is a polyarticular inflammatory joint disease that affects primarily the small joints of the hands and feet. About 1% of the adult population suffers from RA, but there are variation depending on race and continent (Silman and Pearson 2002). The prevalence of RA in whole Finland is about 0.8% (Aho et al. 1998) and in the area of Tampere 0.7% (Korpela 1993) of the population. The risk of RA increases with age, but the disease can appear at any age, though commonly at the age of 40-70 years (Doran et al. 2002a). A shift towards older onset age has been described (Aho et al. 1998). The annual incidence of RA has been reported to be 34/100 000 in Finland (Kaipiainen-Seppanen and Aho 2000), 26/100 000 in Oslo, Norway (Uhlig et al. 1998) and 45/100 000 in Minnesota, USA (Doran et al. 2002a). The incidence of RA is higher in women than in men (Uhlig et al. 1998, Kaipiainen-Seppanen and Aho 2000, Doran et al. 2002a). The severity of the disease varies from mild self limiting illness up to aggressive, drug resistant disease which causes joint destruction and deformity leading to severe disability. Life expectancy has been calculated to be reduced from 3 up to 18 years (Pincus and Callahan 1986, Myllykangas-Luosujarvi et al. 1995, Wong et al. 2001), partly because of complications, of which the most common are infections, cardiovascular diseases and, especially in the past, amyloidosis (Immonen et al 2008).

1.2 Classification and treatment response criteria of rheumatoid arthritis

The classification of rheumatoid arthritis (RA) has undergone many steps to arrive at its present status which was devised by American Rheumatism Association (ARA; now American College of Rheumatology, ACR) in 1987 (Arnett et al. 1988). At least four of the seven classification criteria should be fulfilled and symptoms should last at least six weeks to allow making a diagnosis of RA (Table 1).

Table 1. *Classification criteria for rheumatoid arthritis (RA).*

1	Morning stiffness	lasting at least one hour before improvement and duration of at least six weeks
2	Arthritis in at least three joint areas	simultaneous soft tissue swelling or fluid observed by physician in at least three of next areas: PIP, MCP, wrist, elbow, knee, ankle, and MTP joints (right/left)
3	Arthritis of hand joints	swelling/fluid in wrist, MCP, or PIP joints
4	Symmetric arthritis	simultaneous arthritis of the same joints (as mentioned in 2) on both sides of the body (bilateral involvment of PIP, MCP or MTP joints is acceptable without absolute symmetry)
5	Rheumatoid arthritis	subcutaneous nodules observed by a physician
6	Serum rheumatoid factor	detected by a method positive in fewer than 5% of normal controls
7	Radiographic changes	typical radiographic changes of RA on posterior hand and wrist radiographics, must include erosions/unequivocal bony decalcification in / most marked adjacent to the involved joints (OA changes alone do not qualify)

PIP, proximal interphalangeal; MCP, metacarpophalangeal; MTP metatarsophalangeal; OA, osteoarthritis. (Modified from Arnett et al. 1988)

There may be difficulties in diagnosing early RA when all symptoms are not very clear, disease onset is insidious, rheumatoid factor (RF) is negative, typical erosions are lacking, or synovitis occurs predominantly in the lower extremities. Moreover, rheumatoid nodules are detected mainly in advanced seropositive diseases (Mitchell and Pisetsky 2007).

Predictive factors for early RA, like genetic factors, serological markers and methods for detecting early radiographic changes, have been studied to start treatment with effective medication as early as possible. The aim of the treatment

of RA is first to relieve pain and arrest inflammation, to achieve clinical remission as early as possible and to prevent joint destruction (Mitchell and Pisetsky 2007). To define treatment efficacy, two different response criteria are in use to evaluate treatment efficacy; The American College of Rheumatology (ACR) criteria (Felson et al. 1995) and the Disease Activity Score (DAS) (van Gestel et al. 1998, van Gestel et al. 1999) (Table 2). ACR20, ACR50 and ACR70 criteria represent 20%, 50% and 70% improvement in the core set of criteria, respectively. The core set of disease activity measures consists of the tender and swollen joint count, physician's assessment of disease activity (VAS, visual analogue scale, 0-10 cm), patient self-assessed functional disability [e.g. Health Assesment Questionnaire (HAQ)] and patient's assessments of general health and pain and, laboratory evaluation of acute phase reactants [erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)]. ACR20 stands for a 20% improvement in both tender and swollen joint counts and also ≥ 20% improvement in three of the five above mentioned variables (Felson et al. 1995).

Table 2. *American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) response criteria in rheumatoid arthritis (RA).*

	ACR response criteria	EULAR DAS28 criteria
Variables assessed	SJC, TJC, PtGA, PhGA, PtP, PtF, ESR/CRP	SJC28, TJC28, ESR/CRP, GeH
Formation model	Improvement in percentages from baseline of SJC and TJC and 3/5 from remain	0.56 x √(TJC28) + 0.28 x √(SJC28) + 0.7 x Ln(ESR) + 0.014 x GeH(mm VAS)
Response	ACR20/50/70 represent 20%, 50% or 70% improvement from baseline	HDA ≥ 5.1, MDA 3.2-5.1, LDA≤ 3.2
Remission	at least 5/6 of following criteria in 2 consecutive months: morning stiffness ≤ 15 min, no fatigue, no pain, no tenderness in joints, no swelling in joints / tendon-sheaths, ESR < 20 (w) / 30 (m)	<2.6

SJC, swollen joint count; TJC, tender joint count; PtGA/PhGA, patients/physicians global assesment (e.g. VAS); PtP, patients pain assessment (e.g VAS); PtF, patient's functional assesment (e.g. HAQ = health assessment questonnaire); ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; GeH, general health; LDA, low disease activity; MDA, medium disease activity; HDA, high disease activity, w, women; m, men.

DAS28, developed from original DAS response criteria from European League Against Rheumatism (EULAR) (Prevoo et al. 1995) is also used as an

activity and response criteria for RA (van Gestel et al. 1998, van Gestel et al. 1999). DAS28 is calculated with an equation (Table 2) where the following variables are included; count of tender and swollen joints (28 points), erythrocyte sedimentation rate and general health assessed by VAS (Prevoo et al. 1995, van Gestel et al. 1998).

Because of their different purpose of use, DAS and ACR response criteria have differences. DAS was developed to estimate disease activity, and it gives absolute (and not relative) values and changes in the disease activity. In contrast ACR criteria were developed to estimate the effect of drug treatment and they define improvement on the basis of relative (percentage) changes including two different outcome categories, responders and nonresponders. DAS criteria instead include three variations of outcomes; good, moderate and absent. (van Gestel et al. 1999, Mäkinen et al. 2007a).

1.3 Etiopathogenesis of rheumatoid arthritis

The etiopathogenesis of RA includes multiple genetic and environmental factors, which have been investigated. Part of the factors has been specified and some are under investigation. Because of complicated nature of RA, much of the etiology is still unknown.

Genetic factors have been shown to be an important part of the etiology of RA in several studies. Concordance among monozygotic twins (12-15%) has been found to be higher than in dizygotic twins (4%) (Aho et al. 1986, Silman et al. 1993). The heritability of RA in the Finnish population was reported to be 65% (Aho et al. 1986) and in the data from UK it was estimated as 53% (MacGregor et al. 2000). Persons with a sibling with RA have a 2-4% risk of developing the disease as compared to those without RA in the family (Seldin et al. 1999). The major histocompatibility (MHC) locus makes a significant contribution to RA. There are multiple loci that associate with the genetic risk for RA and the MHC locus encodes cell-surface proteins called the human leukocyte antigens (HLAs) which account for 30% to 50% of overall genetic susceptibility to RA (Seldin et al. 1999, Bowes and Barton 2008). There are three types of HLA antigens, class I, II and III, depending on the structure of the

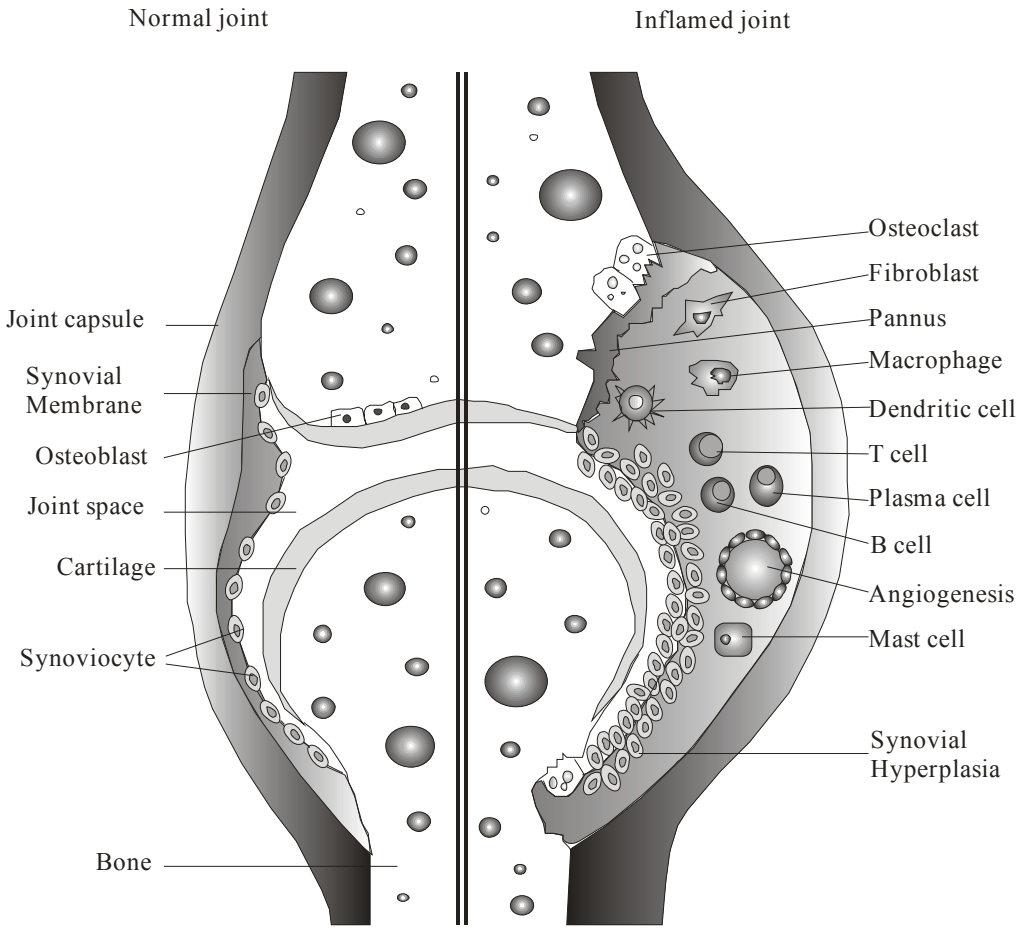

Figure 1. *Structure of a normal and inflamed joint. Modified from Smolen and Steiner 2003.*

In an inflamed joint, the structure is transformed as a result of multiple factors that are involved in the pathologic process in the joint (Figure 1). Inflamed synovium is converted into histologically differentiated pannus as a result of the presence of different inflammatory cells and mediators. When the disease progresses the pannus invades the cartilage and covers the articular bone resulting in cartilage and bone erosions. Cartilage destruction involves cytokines, matrix metalloproteases (MMPs) and other mediators that inflict dysregulation of chondrocytes and also affect directly articular cartilage by degrading it (Goldring 2003). As the disease further progresses, the cellular pannus can be replaced by fibrous pannus. Pannus and mediators produced by the pannus tissue result also in bone erosions, were the imbalance between bone formation and resorption progressively leads to focal bone loss (Goldring 2003). Tumor necrosis factor alpha (TNFα) and interleukin 1 (IL-1) and 6 (IL-6) are regarded as key factors

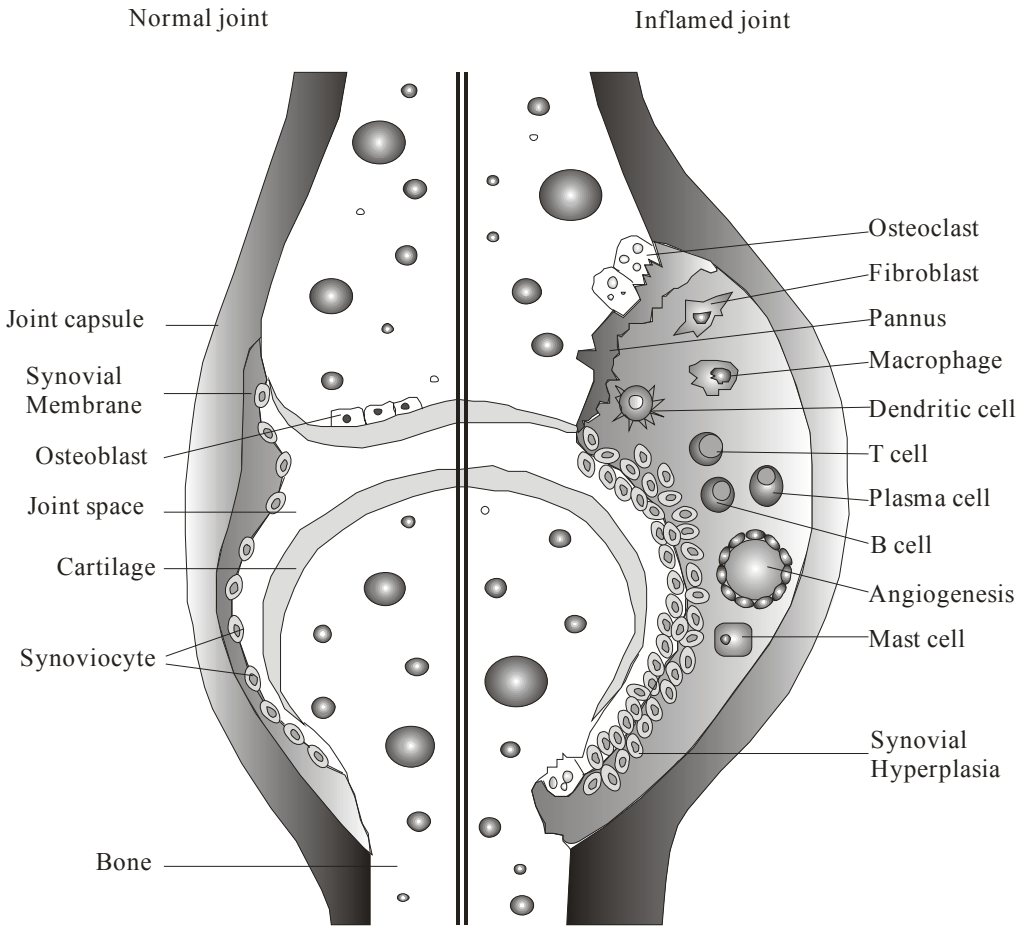

Figure 1. *Structure of a normal and inflamed joint.*

In an inflamed joint, the structure is transformed as a result of multiple factors that are involved in the pathologic process in the joint (Figure 1). Inflamed synovium is converted into histologically differentiated pannus as a result of the presence of different inflammatory cells and mediators. When the disease progresses the pannus invades the cartilage and covers the articular bone resulting in cartilage and bone erosions. Cartilage destruction involves cytokines, matrix metalloproteases (MMPs) and other mediators that inflict dysregulation of chondrocytes and also affect directly articular cartilage by degrading it (Goldring 2003). As the disease further progresses, the cellular pannus can be replaced by fibrous pannus. Pannus and mediators produced by the pannus tissue result also in bone erosions, were the imbalance between bone formation and resorption progressively leads to focal bone loss (Goldring 2003). Tumor necrosis factor alpha (TNFα) and interleukin 1 (IL-1) and 6 (IL-6) are regarded as key factors

driving rheumatoid inflammation in the joint which eventually leads to erosions and joint destruction (Feldmann et al. 1996, Feldmann 2009).

1.3.2 Inflammation

The inflammatory reaction is a fundamental process and a defence mechanism of the body against any insult toward tissues e.g. microbes or mechanical or thermal or chemical damage. The intention is to isolate, dilute or destroy the invading agent or repair the injury, if possible. The inflammatory site is characterized by vasodilatation of blood vessels and increased permeability of the microcirculation which in turn leads to excessive transmigration of leukocytes, plasma proteins and interstitial fluid (Kumar et al. 2004).

In RA, the inflammation is prolonged and the prominent cells originate from monocytic cell line, not the neutrophilic cell line as in acute inflammation. Although the cellular reaction differs between acute and chronic inflammation, the classical signs of inflammation, *calor* (heat), *dolor* (pain), *rubor* (redness) and *tumor* (swelling) are apparent also in the chronic type of inflammation (Kumar et al. 2004). In the rheumatic joint, the inflammation is localized especially in synovium where a number of different cells are activated and involved in various pathological processes. In the inflamed synovium, the main cells involved in the hyperplasia of synovial lining are type A (macrophage-like) and type B (fibroblast-like) synoviocytes. The number of cells is increasing and the tissue undergoes changes in morphology due to influx of mononuclear cells like T cells, B cells, macrophages, and plasma cells. Endothelial cells of synovial blood vessels become activated by different inflammatory mediators and permeability as well as neovascularisation is increased. Leukocyte excavation is increased due to the action of the different groups of adhesion molecules which allow leukocytes to gain access to the inflamed tissue (Firestein 2003, Sweeney and Firestein 2004).

In the innate immune system, different cells, like dendritic cells and macrophages, express toll-like receptors which bind various foreign and self structures and become activated. Activated toll-like receptors further activate the cells of the adaptive immune system (Smolen et al. 2007).

It is assumed that arthritis associated antigens are presented to T cells by antigen-presenting cells (APC), like macrophages, dendritic cells and activated B cells which for their part are activated by foreign or self peptides. In order to achieve maximum activation, T cells require two distinct signals, the antigen specific signal and the co-stimulatory signal, which are both carried by APC. In antigen specific signalling, a surface molecule of MCH class II is acting as an epitope and interacts with the T cell receptor of $CD4^+$ T cell. In addition, in co-stimulatory signalling, APC activates $CD4^+$ T cell via CD80/86 that bind CD28 expressed by T cells (Smolen et al. 2007, Korhonen and Moilanen 2009a). The group of stimulated T cells are mainly formed from T-helper 1 cells that after stimulation release different modulators to activate macrophages, B cells, fibroblasts and osteoclasts inducing in turn many different pathological changes. Activated B-cells differentiate into plasma cells and secrete autoantibodies like RF that are able to form immune complexes stimulating production of proinflammatory cytokines, like TNFα (Smolen et al. 2007).

In addition to inflammatory cells, cytokines play a key role in the pathogenesis of chronic inflammatory diseases including RA, SpA and juvenile idiopathic arthritis (JIA). Micro-array data has revealed that chronic arthritis alters the expression of more than 400 genes including a number of genes regulating the expression cytokines and adhesion molecules (Adarichev et al. 2005). In arthritis, cytokines are expressed and secreted, mainly by leukocytes, synovial cells and chondrocytes. Cells and tissues have variable amounts of cytokine receptors and the effect of a certain cytokine depends not only on the level of the expression of the cytokine in question but also on the level of the expression of its receptors and endogenous antagonists (Feldmann and Maini 2001). Cytokines have also systemic effects and many of these compounds can be measured in the blood (Cassim et al. 2002).

Cytokines are classified as being either pro-inflammatory or anti-inflammatory according to their predominant actions in inflammation, and the outcome and symptoms of the inflammatory reaction depend on the balance between pro-inflammatory and anti-inflammatory cytokines (Feldmann et al. 1996, Feldmann and Maini 2001, Brennan and McInnes 2008). In general, the levels of pro-inflammatory cytokines are higher in the active than in the inactive

phase of RA (Cope et al. 1992, Steiner et al. 1995, Klimiuk et al. 2003a, Klimiuk et al. 2003b), and a fact that has been shown to be true also in JIA (Rooney et al. 1995, Mangge and Schauenstein1998, Yilmaz et al. 2001, Ou et al. 2002).

TNFα is an important proinflammatory cytokine that is involved in local and systemic inflammation and joint destruction in arthritis (Brennan et al. 1992, Feldmann and Maini 2001). However, there is an overlap between the actions of different cytokines. Thus it is of interest that inhibition of a single cytokine, TNFα, results in a profound anti-inflammatory and antierosive effect in patients with arthritis. This may be explained by the concept that TNFα is at the top of the cytokine cascade and regulates directly or indirectly the expression and activity of several cytokines and other inflammatory factors (Feldmann et al. 1996, Feldmann and Maini 2001). However, the networks regulated by TNFα *in vivo* are not known in detail. In addition, it is not known which cytokines and inflammatory factors are associated with a favourable clinical response to the treatment with TNFα antagonists and which factors are related to a poor response or adverse events, and could be used to predict the clinical response to the treatment with TNFα antagonists in individual patients.

2 Spondyloarthropathies

Spondyloarthropathies (also called spondyloarthritides) are a group of diseases consisting of inflammatory conditions described with certain clinical features such as inflammatory back pain (especially sacroiliitis), asymmetrical peripheral oligoarthritis (predominantly in the lower limbs), dactylitis, enthesitis, and specific manifestations including uveitis, psoriasis, and chronic inflammatory bowel disease. In clinical terms, one can differentiate five subgroups; ankylosing spondylitis (AS), psoriathic arthritis (PsA), spondyloarthropathies associated with inflammatory bowel disease (IBD) (ulcerative colitis, UC or Crohns disease, CD) reactive arthritis (ReA) and undifferentiated SpA with AS being the most prevalent (Braun et al. 2005).

The classification criteria of AS was originally developed in 1961 and is known as the Rome Criteria. It has been modified and modernized, the latest

updated version are the New York criteria published in 1984 (van der Linden et al. 1984) (Table 3).

According to the commonly used New York criteria (van der Linden et al. 1984), AS can be definitely diagnosed if at least one criterion of the three criteria is fulfilled in addition to positive radiologic finding indicative of sacroiliitis (Table 3). However, inflammation in sacroiliac joints may not be detected in plain radiographs in the early stages of the disease and appear later, even five to ten years after the first symptoms of the disease. Pathological changes in sacroiliac joints can be detected in its early stages by magnetic resonance imagine (MRI). Since effective biologicals are nowadays available for the treatment of SpA, also minor inflammatory changes should be visualized and it is recognized that MRI is more sensitive than radiographic imaging (Braun et al. 2002b).

Table 3. *The modified New York criteria for inflammatory back pain.*

Clinical criteria
1. Low back pain and stiffness > 3 mo that improves only with exercise, not with rest
2. Limitation in movement of lumbar spine in sagittal and frontal planes
3. Limitation of movement of chest compared with standard range in same age and sex
Radiological criteria
at least grade 2 bilateral sacroilitis or
grade 3-4 unilateral sacroilitis
Definite AS if radiological and at least 1 clinical criteria are fullfilled
Possible AS if
a) three clinical criteria are fullfilled
b) radiological criteria are fullfilled

AS, ankylosing spondylitis. Modified from van der Linden S et al. 1984

As a group, the prevalence of SpA is estimated to be similar to that of RA in Europe (Akkoc 2008). As stated the most frequent disease in the group is AS and it has a prevalence of 0.1-1.4 % in the European population (Braun and Sieper 2007). The annual incidence of AS varies extensively, from 0.5 to 14 per 100 000 individuals. Inflammation of sacroiliac joints is the main manifestation causing low back pain and stiffness, especially in the early morning or after long lasting rest. Other types of the spinal articulations, the discovertebral, facet, costovertebral and costotransversal joints can also be inflamed. Axial disease may be accompanied by peripheral arthritis, most commonly in hip and shoulder

joints, and also in manifestations e.g. enthesitis, dactylitis, and skin and eye involvement (Braun and Sieper 2007).

The cause of SpA is unclear but strong genetic connection has been recognized, especially in AS, in which the connection is mainly explained by the HLA-B27 antigen. In 90-95% of the patients with AS are positive for HLA-B27, but in HLA-B27-positive individuals the risk of developing the disease is about 5%, and substantially higher in HLA-B27-positive relatives of AS patients (Reveille et al. 2005, Sieper 2006, Braun and Sieper 2007). HLA-B27 molecule is found in up to 70% of patients with ReA and 60% with PsA (Reveille et al. 2005). Overall, the genes in the whole MHC, account for about half of the genetic risk. In addition to microbial antigens (i.e. salmonella, yersinia, campylobacteria, klebsiella) environmental factors have been postulated to be possible triggers of the disease (Khan 2002).

In AS, the cartilaginous structures of sacroiliac joints and intervertebral discs are most often the targets of mononuclear cells. The invading T cells and macrophages cause inflammation leading to destruction and ankylosis of different parts of vertebra. In addition, the activities of osteocytes and osteoclasts result in bone remodelling and squaring of vertebral bodies (Braun and Sieper 2007). There is also evidence that TNFα is found in the sacroiliac joints in excess amounts, and therefore it is logical to consider the use of TNFα antagonists in the treatment of SpA (Braun and Sieper 2007).

The initial drug treatment of AS is traditionally based on nonselective NSAIDs and coxibs which inhibit prostaglandin production (Karjalainen et al. 2005, Furst et al. 2007). NSAIDs have been reported to reduce radiological changes if they are used continuously in AS patients (Wanders et al. 2005). DMARDs, especially sulfasalazine and in some cases methotrexate belongs to the drug treatment arsenal (Karjalainen et al. 2005, Furst et al. 2007). The response to gold salts and antimalarial drugs is limited and azathioprine does not seem to be efficacious. Corticosteroids are used in both oral and intra-articular forms. Since increased activity of osteoclasts is involved in the pathogenesis of SpA, bisphosphonates are used in disease treatment due to their ability to inhibit osteoclasts and because of their anti-inflammatory effects in chronic inflammation. The clinical response to drug treatment for AS can be assessed by

using BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and BASFI (Bath Ankylosing Spondylitis Functional Index) indexes (Table 4). Treatment is regarded as ineffective if the reduction of BASDAI index is less than 50% or less than 2 cm (Dougados et al. 2002, Karjalainen et al. 2005, Furst et al. 2007).

Table 4. *Questions to patients with ankylosing spondylitis (AS) to evaluate disease activity and functional ability during the past week*

BASDAI	1	Describe your overall level of fatigue/tiredness
	2	Describe your overall level AS neck, back or hip pain
	3	Describe your overall level of pain/swelling in joints other than neck, back or hips
	4	Describe your overall level of discomfort of any areas tender to touch or pressure
	5	Describe your overall level of morning stiffness from the time you wake up
	6	How long does your morning stiffness last from the time you wake up*
BASFI	1	Putting on your socks or tights without help or aids (e.g. sock aid)
	2	Bending from the waist to pick up a pen from the floor without aid
	3	Reaching up to a high shelf without help or aids (e.g. helping hand)
	4	Getting up from an armless chair without your hands or any other help
	5	Getting up off the floor without help from lying on your back
	6	Standing unsupported for 10 minutes without discomfort
	7	Climbing 12-15 steps without using a handrail or walking aid
	8	Looking over your shoulder without turning your body
	9	Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports)
	10	Doing a full days activities whether it be at home or at work

*BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; VAS 0-10 cm; 0, none and 10, worst; *scale 0-2 hours. Equation for BASDAI index: [(1+2+3+4) + (5+6) / 2] / 5, resulting a final score 0-10.*
BASFI, Bath Ankylosing Spondylitis Functional Index; VAS 0-10 cm; 0, easy and 10, impossible. Equation for BASFI index: (1+2+3+4+5+6+7+8+9+10) / 10, resulting a final score 0-10.

In IBD (CD or UC) associated arthritis, drug treatment is based greatly on the patient's clinical symptoms and tailored individually. Symptomatic treatment with NSAIDs is problematic because of their possible ability to activate IBD (Rudwaleit and Baeten 2006). Glucocorticoids are also used, but only to assist and strengthen other drug treatment. Some DMARDs may be used in the treatment of IBD, but their efficacy is not always adequate and adverse events may occur. TNF antagonists (infliximab and adalimumab) have been found to be effective and well tolerated in the treatment of IBD associated arthritis (Collins and Rhodes 2006, Clark et al. 2007, Cummings et al. 2008).

In PsA, NSAIDs are often used to relieve symptoms of SpA as are glucocorticoids which may be administered both orally and locally. DMARDs are moderately effective, but TNFα therapy (infliximab, etanercept and

adalimumab) has been shown to be both effective and antierosive (Feuchtenberger et al. 2008).

In Finland, biological drug treatment in AS patients is usually initiated if the patient has an active disease based on BASDAI index and clinical findings (acute sacroiliitis, elevated acute phase reactants, MRI findings) despite treatment with at least two different NSAIDs for at least three months and sulfasalazine (or possibly other DMARDs) treatment has proved to be ineffective after at least four months of treatment (Karjalainen et al. 2005). In the other SpA conditions, like PsA or IBD associated arthritis, there are no defined criteria as to when biologicals should be started, and the decision to initiate treatment is made on clinical grounds based on the severity of the arthritis and inflammatory axial disease, and based on clinical criteria, often those used in RA and SpA (Karjalainen et al. 2005).

3 Juvenile idiopathic arthritis

JIA is defined as chronic inflammatory arthritis in children starting before 16 years of age. It may cause disability in the early phase of the disease and later in the children's development. Prevalence of JIA depends on the continent, area of study and paediatric population, varying from 7 up to 400 per 100.000 children (Gäre and Fasth 1992, Moe and Rygg 1998, Manners and Bower 2002). The annual incidence of JIA has been reported to vary between 2 to 23 per 100.000 (Manners and Bower 2002). In Finland, the incidence of JIA has been reported to vary between 15 to 23 per 100.000 (Kaipiainen-Seppanen and Savolainen 2001).

JIA encompasses various types of chronic arthritis in childhood or adolescence starting below the age of 16 years; in which the cause of arthritis remains unknown and symptoms have lasted at least six weeks. Several different classifications have been developed for JIA, but the International League of Associations for Rheumatology (ILAR) classification (Petty et al. 2004) is nowadays most commonly used (Table 5).

Table 5. *Subtypes of juvenile idiopathic arthritis (JIA) based on the second revision of International League of Associations for Rheumatology (ILAR) criteria.*

Subtype	Clinical feature
Oligoarthritis	Arthritis in 1-4 joints during the 1st 6 months
Persistent	Affects < 5 joints throughout disease
Extended	Affects > 5 joints after the 1st 6 months
Polyarthritis	Arthritis in > 5 joints during 1st 6 months
Seronegative	RF-negative
Seropositive	RF-positive at least 2 times minimum 3 months apart during the 1st 6 months
Systemic arthritis	Arthritis in > 1 joints with or prior to 2-week fever and > 1 of next: -Erythematous nonfixed rash -Generalized lymph node enlargement -Hepato-and/or splenomegalo -Serositis
Enthesitis related arthritis	Arthritis and enthesitis, or arthritis or enthesitis with >2 of next: -Present or history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain -Presence of HLA-B27 -Onset of arthritis in males aged <6 years -Acute symptomatic anterior uveitis -History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in 1st degree relative
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and > 2 of next: -Dactylitis -Nail pitting or onycholysis -Psoriasis in 1st degree relative

Modified from Petty et al. 2004.

As mentioned above, JIA is a heterogenous group of inflammatory conditions of unknown cause, but genetic component has been studied (Ravelli and Martini 2007). Due to the heterogeneity, the drug treatment also varies between the different subtypes of JIA. Like in RA, symptomatic treatment of JIA includes NSAIDs and glucocorticoids dosed orally (Ravelli and Martini 2007), or intra-articularly (Breit et al. 2000). In systemic onset JIA the drugs can even be administered parenterally (Adebajo and Hall 1998). In addition to chronic arthritis itself, also glucorticoid treatment might cause growth retardation (Ravelli and Martini 2007). DMARDs used in RA are usually adopted for clinical use also in the treatment of JIA. The most often used DMARD is methotrexate, which has been reported to be effective in the treatment of JIA

(Giannini et al. 1992, Ruperto et al. 2004). Sulfasalazine (van Rossum et al. 1998, van Rossum et al. 2007), leflunomide (Silverman et al. 2005a, Silverman et al. 2005b) cyclosporine A (Ostensen et al. 1988, Reiff et al. 1997, Gerloni et al. 2001, Ravelli et al. 2002) and azathioprine (Kvien et al. 1986, Savolainen et al. 1997) have also been examined and found to be effective. Hydroxychloroquine (Brewer et al. 1986), aurothiomalate (gold sodium thiomalate, GSTM) (Brewer et al. 1980), and auranofin (Giannini et al. 1990, Giannini et al. 1991) have been found to be well tolerated but their efficacy is less certain.

The criteria and definition of improvement in JIA, ACR pediatric response criteria (ACR Pedi) have similarities with adult RA, i.e. ACR Pedi30, ACR Pedi50 and ACR Pedi70 are usually assessed (Giannini et al. 1997). As in adult RA, clinical remission or inactive disease are the main targets of the drug treatment (Wallace et al. 2004).

4 Drug treatment of rheumatoid arthritis and spondyloarthropathies

The nature of RA is multifactorial and there is extensive variation in the progression of the disease between different individuals. For this reason, the treatment of RA is challenging. In the treatment of RA, the main objective is to relieve pain, attenuate inflammation and prevent the destruction of joints to achieve clinical remission, and maintain functional capacity and working ability (Möttönen et al. 1999, Korpela et al. 2004, Puolakka et al. 2005, Puolakka et al. 2006, Mäkinen et al. 2007b, Rantalaiho et al. 2009).

In Finland, the treatment of RA is based on the national recommendations (Rheumatoid arthritis: Current Care Guidelines 2009), which recommend that active DMARD treatment should be initiated immediately after the diagnosis. The drug treatment to be used varies between different patients and must be individually planned. The initial pharmacological treatment includes NSAIDs, combined with one or more DMARDs, and with oral glucocorticoids if needed. The first line DMARD treatment in RA is methotrexate. If methotrexate causes

adverse events or is not effective enough, another DMARD (hydroxychloroquine, sulfasalazine, leflunomide, azathioprine, and cyclosporine) can be used or combined with the methotrexate treatment. Combination therapy with methotrexate, sulfasalazine and hydroxychloroquine is recommended in early RA since combination therapy with two or more DMARDs has been shown to reduce the radiologic progression and patients achieve more often clinical remission compared to patients treated with a single DMARD (Möttönen et al. 1999, Mäkinen et al. 2007b, Rantalaiho et al. 2009) The benefit of early effective combination therapy can be seen in the long term, even if the patient's subsequent drug treatment is restricted (Möttönen et al. 1999, Korpela et al. 2004, Mäkinen et al. 2007b, Rantalaiho et al. 2009). Early suppression of disease activity with combination therapy has also been shown to be beneficial to the patient's working capacity (Puolakka et al. 2005, Puolakka et al. 2006).

In AS, drug treatment is based initially on NSAIDs and DMARDs, most often sulfasalazine (Karjalainen et al. 2005, Furst et al. 2007). A TNFα antagonist is added to ongoing drug treatment if it is not effective enough or if the traditional DMARDs cause adverse reactions (Rheumatoid arthritis: Current Care Guidelines 2009, Karjalainen et al. 2005). In the present study, combination DMARD treatment is used in combination with anti-TNFα therapy, not simply with one DMARD as is the case in most other international recommendations and clinical studies.

4.1 Symptomatic treatment

In the treatment of RA, NSAIDs and glucocorticoids form the foundation of the symptomatic treatment. NSAIDs are the very first drug treatment used in the treatment of rheumatoid diseases. Their ability to inhibit the synthesis of prostaglandins results in analgesia and may suppress inflammation. NSAIDs are recommended to be used at the lowest effective doses. With respect to the adverse events, gastrointestinal (GI) problems are less frequently encountered in RA patients treated with paracetamol (acetaminophen) than with the nonselective NSAIDs, but there is no difference in GI problems when RA patients are treated with coxibs (Tannenbaum et al. 2006). Topical NSAIDs can be tried especially if

oral NSAID preparations are contraindicated either because of adverse effects or because the patient is in a high risk group or paracetamol is insufficient (Tannenbaum et al. 2006). NSAIDs can be combined with a proton pump inhibitor to avoid GI problems, especially in patients with increased risk. No statistically significant differences have been found in the efficacies of the various NSAIDs (Gotzsche and Johansen 2004). Coxibs are as effective as nonselective NSAIDs or paracetamol for the symptoms of arthritis, but individual differences exist (Ong et al. 2007). The advantages of coxibs are their less marked GI effects, but there is no difference between these drugs and their traditional counterparts in terms of their renal or blood pressure effects (Tannenbaum et al. 2006).

Over the past five decades, glucocorticoids have been used in the treatment of RA. Although new therapies have been introduced, glucocorticoids have maintained their primary position and are still in wide use. Their distinctive anti-inflammatory and immunomodulary effects in the treatment of RA might be one reason for favouring their continued use (Buttgereit et al. 2005). In clinical studies, they have been reported to relieve inflammatory symptoms and glucocorticoids are recommended to be added to DMARD treatment if DMARDs are not effective on their own (Gotzsche and Johansen 2004). In the study with four different treatment strategies (BeSt study), glucocorticoids were found to be comparable to infliximab in the treatment of early RA when used in addition to DMARD mono- or combination therapy to inhibit the radiographic progression and as a way of enhancing the functional improvement (Goekoop-Ruiterman et al. 2005).

The limiting factor in treating RA with glucocorticoids is their adverse effects. For example, in RA the risk of osteoporosis is enhanced and glucocorticoid treatment further worseness this situation. Other musculoskeletal adverse effects in addition to osteoporosis are myopathy and osteonecrosis. Glucocorticoids alter glucose metabolism and increase blood glucose levels in a dose dependent manner. Even intra-articularly dosed glucocorticoids can cause hyperglycaemia. Glucocorticoid treatment in RA patients even with low doses has been found to increase body weight, probably because of the effects of these drugs on glucose metabolism. The risks of dyslipidaemia, atherosclerosis and

cardiovascular diseases are not clearly elevated by lower doses, but with higher doses (prednisolone > 10 mg/day) the risk does increase in a dose dependent manner. Since they have also mineralocorticoid effect, hypernatremia, hypokalemia and oedema may be seen in patients treated with glucocorticoids. RA patients have an increased risk to develop GI lesions, even bleeding ulcer due to NSAIDs, and glucocorticoid treatment further increases that risk. Cataract and glaucoma have also reported as adverse effects of glucocorticoids. The increased risk of infections is also linked to glucocorticoid treatment (Da Silva et al. 2006, Hoes et al. 2008).

4.2 Non-biological disease modifying antirheumatic drugs

Only a few decades ago, RA was a severe disease with no real hope of cure. Since that time, the drug treatment of RA has seen many revolutionary discoveries and improvements and modern drug treatment can prevent more effectively the progression of the disease and development of erosions, and improve the functional performance.

Table 6. *Disease modifying antirheumatic drugs (DMARDs) used in the treatment of rheumatoid arthritis (RA) and spondyloarthropathies (SpA).*

Medicine	Dose	Action of mechanism	Adverse effect
Methotrexate	7.5-25 mg p.o./i.m./s.c. /week	many different hypotheses	gastrointestinal symptoms, nausea, stomatitis, alopecia, blood marrow suppression and abnormalities in liver function
Sulfasalazine	first 1 g/day p.o., then 2-3 g/day	exact mechanism is not known	hypersensitivity, liver function abnormalities, gastrointestinal effects and rarely mild cytopenias
Hydroxychloroquine/ chloroquine	200-400 mg/day p.o. (max 600 mg/day)	exact mechanism is not known	retinal toxicity
Leflunomide	10-20 mg/day p.o.	inhibition of pyrimidine biosynthesis	gastrointestinal complaints, diarrhea, temporary alopecia, elevation of transaminases
Azathioprine	first 50 mg/day, then 2-2.5 mg/kg/day	inhibition of purine synthesis and DNA replication	GI involvements, nausea, elevation of transaminases
Cyclosporine	2.5-4 mg/kg/day	inhibition of phosphatase calcineurin	nephrotoxicity, nervous system, skin and GI involvements
Gold compounds			
Auranofin	6 mg/day in p.o. in 2 doses, after 3 months dose elevated ad 9 mg/day in 3 divided doses	exact mechanism is not known	diarrhea, rash, stomatitis, proteinuria, changes in blood count, polyneuropathy
Gold sodium thiomalate	first 10 mg i.m., then 50 mg/week until response (ad 13mg/kg) is achieved, then 50 mg once a month		rash, stomatitis, proteinuria, changes in blood count, polyneuropathy

4.2.1 Methotrexate

Methotrexate (Table 6) is probably the most widely used anti-rheumatic drug in the treatment of RA particularly because of its good efficacy and safety. It was initially used in the treatment of RA in the 1980's (Thompson et al. 1984, Weinblatt et al. 1985, Williams et al. 1985) and its use vastly increased in the 1990s (Sokka et al. 1997, Klaukka and Kaarela 2003). In long term clinical studies up to 15 years, methotrexate has generally been found to be both efficacious and safe (Weinblatt et al. 1994, Sokka and Hannonen 1999), and today methotrexate has an established role in the treatment of RA.

Methotrexate is generally administered to RA patients as a single weekly dose (7.5-25 mg/week) given either orally or subcutaneously (Rheumatoid arthritis: Current Care Guidelines 2009). The exact mechanisms of the anti-inflammatory action of methotrexate are still unclear and several hypotheses have been presented (Cronstein 2005). Firstly, methotrexate was believed to be a compound which could inhibit the proliferation of inflammatory cells in rheumatoid synovia, because of its antifolate properties. Secondly, the effects of methotrexate were explained by its ability to inhibit the accumulation of polyamines which contribute to tissue injury in RA. A third possible mechanism of action of methotrexate is its reducing effect on the levels of intracellular gluthathione which in turn leads to inhibition of the actions of macrophages and lymphocytes. In addition, the effects of methotrexate have recently been claimed to be mediated through adenosine (Cronstein 2005). Although methotrexate is generally well tolerated, its adverse effects include GI symptoms, nausea, abnormalities in liver function, stomatitis, alopecia and bone marrow suppression (Cronstein 2005, Rheumatoid arthritis: Current Care Guidelines 2009).

4.2.2 Sulfasalazine

Sulfasalazine (Table 6) was developed for the treatment of RA in the 1940s. Its sulfapyridine was originally believed to affect the infectious component of RA and salicylate portion of the molecule believed to relieve pain and stiffness. Although sulfasalazine has been in use for a long time, its exact mechanism of

action is still unknown. The action of sulfasalazine in RA has been considered to be mediated by different immunomodulatory and anti-inflammatory mechanisms. It has immunomodulatory effects, for example *in vitro* studies have shown sulfasalazine to inhibit expression of cytokines, e.g. TNFα, in addition to inhibition of different cellular responses. In *in vivo* studies, sulfasalazine has been found to depress type II collagen-induced arthritis. Sulfasalazine has several potential anti-inflammatory effects, i.e. it has been shown to inhibit the migration of inflammatory cells, prevent the production of proteolytic enzyme and chemotaxis (Plosker and Croom 2005). Sulfasalazine is used in the treatment of RA as mono- and combination therapy. Adverse effects are mainly hypersensitivity to sulphonamides, minor GI effects, rash and headache, rarely cytopenias (agranulocytosis) (Doan and Massarotti 2005, Plosker and Croom 2005).

4.2.3 Antimalarial drugs

Two antimalarial drugs, hydroxychloroquine sulphate and chloroquine phosphate (Table 6), are used in the treatment of RA. Because of its minor toxicity, hydroxychloroquine is preferred in spite of its lesser effectivity. In general, antimalarials have a mild effect when used alone, but hydroxychloroquine is often used as a component of combination therapy with other DMARDs (Möttönen et al. 1999, Korpela et al. 2004, Doan and Massarotti 2005, Mäkinen et al. 2007b, Rantalaiho et al. 2009, Rheumatoid arthritis: Current Care Guidelines 2009).

4.2.4 Leflunomide

Leflunomide (Table 6) differs from other DMARDs in its structure and mechanism of action. It inhibits pyrimidine biosynthesis resulting in an anti-proliferative effect, which in RA targets especially activated lymphocytes. Since it is a prodrug, it must be metabolized to an active compound and it enters the enterohepatic circulation which prolongs its half-life to approximately 15 days. Leflunomide is effective in the treatment of RA; the most commonly

encountered adverse events are diarrhea, nausea, alopecia and abnormalities in liver function tests (Breedveld and Dayer 2000, Cannon and Kremer 2004).

4.2.5 Cyclosporine

The action of cyclosporine (Table 6) consists of mainly inhibition of phosphatase calcineurin which in turn inhibits cytokine production in activated lymphocytes. Due to its ability to inhibit the production of inflammatory mediators, cyclosporine can suppress joint inflammation and bone and cartilage destruction. Cyclosporine has been shown to be effective in monotherapy as well as combined with other DMARDs and it is indicated for the treatment of refractory RA. Unfortunately, adverse effects (nephrotoxicity, nervous system disturbances, skin and GI problems) may require the termination of treatment (Kitahara and Kawai 2007).

4.2.6 Gold compounds

Before the discovery of methotrexate, gold compounds were widely used in the treatment of RA. Previously, the most commonly used gold compound was intramuscularly administered gold sodium thiomalate (Table 6) (Clark et al. 1989). An oral compound, auranofin, is also available. With both oral and intramuscular dosing, the therapeutic effect develops slowly and because of potential toxicity the treatment is started with ascending doses (Doan and Massarotti 2005). Only gold sodium thiomalate has been shown to retard radiological progression and it was shown to be disease-modifying in the long time (Luukkainen et al. 1977a, Luukkainen et al. 1977b). The exact mechanism of action of gold is not known (Doan and Massarotti 2005), but recent findings implicate the inflammatory mitogen-activated protein (MAP) kinases signalling pathway as a target of aurothiomalate (Nieminen et al. 2008).

4.2.7 Azathioprine

Azathioprine (Table 6) is an immunosuppressive drug that has been used also in the treatment of RA as an alternative to methotrexate therapy. The efficacy of the azathioprine is comparable to the other DMARDs. However, it causes serious adverse events (elevation in transaminases, cytopenia, opportunistic infections), which limit its use to cases when the patient fails to respond to other DMARDs (Suarez-Almazor et al. 2000).

4.2.8 Combination therapy

Combination therapy with two or more DMARDs simultaneously in the treatment of refractory RA is often used in Finland (Möttönen et al. 1999, Mäkinen et al. 2007b, Rantalaiho et al. 2009) and has been found to be effective also in other clinical studies (Boers et al. 1997, Landewe et al. 2002, Goekoop-Ruiterman et al. 2005, Allaart et al. 2006). Methotrexate is the anchor drug in the combination therapy. The most commonly used combination is methotrexate, sulfasalazine and hydroxychloroquine. A low-dose prednisolone is added to the above combination if needed. Combination DMARD treatment of early RA has been shown to prevent the long-term radiological changes (Korpela et al. 2004). In addition, biological drug is usually combined with one or more DMARDs, most often with methotrexate.

4.3 Biological disease modifying antirheumatic drugs

Due to the multifactorial nature of RA, even combination therapy is not always effective enough. Biological DMARDs (Table 7) represent the modern treatment of inflammatory diseases. They have established their position in rheumatology and are now widely used. Different biological drugs are available depending on the main target of the treatment, i.e. antibody against TNFα, IL-1R, CD20 antigen expressed in B lymphocytes, IL-6 receptor or fusion protein binding to TNFα or CD80/86 molecules on antigen-presenting cells.

Table 7. *Biological disease modifying drugs used in the treatment of rheumatoid arthritis (RA) and spondyloarthropathies (SpA).*

Medicine	Dosage	Trade name	Structure	Mechanism of action
Infliximab	3-10 mg/kg i.v., first at weeks 0, 2, 6, thereafter about 8 week intervals	Remicade®	chimeric monoclonal ab	TNFα inhibitor
Etanercept	50 mg s.c. weekly	Enbrel®	soluble TNF alpha receptor fusion protein	TNFα inhibitor
Adalimumab	40 mg s.c. at two week intervals	Humira®	humanised monoclonal ab	TNFα inhibitor
Anakinra	100 mg s.c. daily	Kineret®	recombinant soluble human IL-1 receptor antagonist	IL-1 receptor antagonist
Rituximab	500-1000 mg i.v. twice at two week intervals	Mabthera®	chimeric CD-20-ab	depletion of B cells
Abatacept	10 mg/kg i.v. at four week intervals	Orencia®	CTLA-4-immunoglobulin complex	inhibition of T cell activation
Tocilizumab	8 mg/kg i.v. at 4 week intervals	Roactemra®	humanised monoclonal ab	IL-6 receptor antagonist

4.3.1 Anti-TNFα therapy

The proinflammatory cytokine TNFα was discovered in the 1970s and it was appreciated as the central mediator in the cytokine network in the pathogenesis of RA. It was also found to bind to two receptors, the type I TNF receptor (p55) and the type II TNF receptor (p75). This was followed by the development of TNFα antagonists, which were able to inhibit the actions of TNFα either through a monoclonal antibody against TNFα or through a soluble receptor for TNFα. At the moment there are three different TNFα antagonists in clinical use, infliximab, etanercept and adalimumab, all of which were studied in the present study. They have demonstrated their anti-inflammatory and antierosive effects in RA and they have displayed also efficacy in JIA and SpA. The mechanism of action and different applications in clinical studies are explained in more detail below (chapter 5).

Golimumab is a new human anti-TNFα monoclonal antibody. In clinical studies in patients with RA it has been found to be effective with or without traditional DMARD therapy (Zhou et al. 2007, Kay et al. 2008, Keystone et al.

2009). Its efficacy has been studied also in AS (Inman et al. 2008) and PsA (Kavanaugh et al. 2009). No reports about golimumab treatment in JIA patients have been published. The newly developed certolizumab pegol is humanized antibody Fab fragment with specifity for human TNFα and it is a novel treatment of Crohn's disease (Schreiber et al. 2005, Schreiber et al. 2007) and it also has been introduced into the therapy of RA (Keystone et al. 2008, Smolen et al. 2009) if the present TNFα antagonists are not suitable or potent enough.

4.3.2 Anakinra

Anakinra (Table 7) is a non-glycosylated, recombinant human soluble interleukin-1 receptor antagonist (sIL-1Ra). IL-1 is a proinflammatory cytokine which plays a pivotal role in the arthritic joint. The natural inhibitor of IL-1, the interleukin 1 receptor antagonist (IL-1Ra), is cleaved from the cell surface and under normal physiological condition its soluble form (sIL-1Ra) is in balance with IL-1 (Burger et al. 2006). Anakinra is a synthetic analogue of the natural cytokine antagonist and it is given daily at a dose of 100 mg, subcutaneously. In clinical studies, it has been found to be moderately effective and antierosive in the treatment of RA (Bresnihan et al. 1998, Cohen 2002) or JIA (Ilowite et al. 2009) and in systemic JIA (Pascual et al. 2005). In the treatment of AS, anakinra has a moderate effect (Tan et al. 2004).

4.3.3 Rituximab

Rituximab (Table 7) is a chimeric human/mouse monoclonal antibody that targets the CD20 antigen expressed on B lymphocytes. The treatment course in RA is given two times intravenously at two week intervals at a dose of 1000 mg to be repeated on average at 9 months intervals. The depletion of CD20+ B-cells is mediated through several mechanisms (Johnson and Glennie 2001, Maloney et al. 2002, Browning 2006, Korhonen and Moilanen 2009b). Rituximab was primarily approved for the treatment of non-Hodgkin's lymphoma but subsequently was found to be effective in the treatment of RA in patients with a history of failed anti-TNFα therapy. Rituximab was first studied in a small open

label study in RA patients who were treated with methotrexate (Edwards and Cambridge 2001). Since this initial result was promising, clinical studies followed where rituximab was combined with methotrexate or other DMARD and found to be effective in the treatment of RA (Edwards et al. 2004, Emery et al. 2006). There is no published evidence on whether the treatment with rituximab is effective in JIA or AS.

4.3.4 Abatacept

Abatacept (Table 7) is a fusion protein composed of the extracellular domain of human cytotoxic T cell-associated antigen-4 (CTLA-4) linked to a hinge and the CH2 and CH3 domains of the human immunoglobulin G1 (IgG1) (Genovese M 2005). The CTLA-4 domain enables abatacept to bind CD80 and CD86 molecules on antigen-presenting cells, preventing their interactions with T cell CD28 which is needed as a co-stimulatory signal for T lymphocyte activation (Genovese et al. 2005). In addition, abatacept may also inhibit T cells through modulation of tryptophan metabolism in antigen presenting cells (Grohmann et al. 2002). Two publications have reviewed the use of abatacept in the treatment of RA (Buch et al. 2008, Korhonen and Moilanen 2009a). There is no published data about abatacept in the treatment of AS or JIA.

4.3.5 Tocilizumab

Tocilizumab (Table 7) is a humanised anti-human IL-6 receptor monoclonal antibody that inhibits the action of IL-6, an important proinflammatory cytokine in RA. Tocilizumab infusions are given every 4 weeks at a dose of 8 mg/kg usually combined with methotrexate or some other DMARD but it may also be given as monotherapy. In clinical trials, tocilizumab has been found to be effective (Nishimoto et al. 2000, Nishimoto et al. 2003, Nishimoto et al. 2004, Maini et al. 2006, Emery et al. 2008, Genovese et al. 2008, Smolen et al. 2008) and antierosive (Nishimoto et al. 2007). Recently, it has been reported that 66% of the RA patients continued tocilizumab treatment after five years follow-up but 22% of the patients had discontinued due to some adverse event (Nishimoto et

al. 2008). In three studies, tocilizumab has been used successfully also in JIA patients (Woo et al. 2005, Yokota et al. 2005, Yokota et al. 2008). No reports about tocilizumab treatment in AS patients have been published.

5 TNFα in rheumatoid arthritis and spondyloarthropathies

TNFα has proved to be an important inflammatory mediator in RA and SpA. The development of TNFα from being a single cytokine to a significant target of a group of biological drugs has had a major impact on the treatment of RA and SpA and has pioneered development of other types of biological drugs.

TNFα was first identified in 1975 as an endotoxin-triggered glycoprotein which induced necrosis of sarcomas transplanted into mice (Carswell et al. 1975). The structure of the gene encoding human TNFα was described (Nedwin et al. 1985) and cloned in 1985 (Pennica et al. 1985). The fact that TNFα occupied an important position in RA was proved by its increased expression in RA synovial cells (Saxne et al. 1988, Brennan et al. 1989b, MacNaul et al. 1990) and by its potency to induce degradation of cartilage (Dayer et al. 1985) and bone (Bertolini et al. 1986). TNFα was also shown to inhibit synthesis of cartilage matrix components (Saklatvala 1986). Expression of many other proinflammatory cytokines (e.g. IL-1 and IL-6) in active synovial cells of RA patients has shown to increase (Fontana et al. 1982, Houssiau et al. 1988) and by neutralizing TNFα with anti-TNFα antibody can result in a reduced production of those cytokines in synovial cells (Brennan et al. 1982, Butler et al. 1988).

5.1 Biosynthesis of TNFα

A membrane-bound precursor form of TNFα, a transmembrane TNFα (mTNFα), is expressed and produced as a 26 kD cell surface type II polypeptide mainly by activated macrophages and T-lymphocytes but also by other cell types. Increased expression of mTNFα in macrophages and T-lymphocytes is mainly the result of cell activation by various inflammatory stimuli while

mTNFα is expressed constitutively in resting natural killer cells (Caron et al. 1999). mTNFα is further processed by a TNFα-converting enzyme (TACE) (Black et al. 1997) by the cleavage of the membrane-anchoring domain to generate soluble 17 kD mature TNFα that is composed of three identical subunits (Jones et al. 1989). In addition, TACE mediates regulatory functions by releasing TNF receptors from the cell-membrane to produce soluble receptors which can bind TNFα and neutralize its biological activity (Wang et al. 2003).

The synthesis of TNFα is tightly regulated, especially at the post-transcriptional level. In inactive cells, TNFα mRNA is produced at detectable levels but protein levels are barely measurable (Brennan et al. 1989b) and TNFα does not exist in a stored form (Beutler and Cerami 1989). Macrophages, the main source of TNFα, are activated by a variety of stimuli, like bacteria, viruses, cytokines (e.g. IL-1, IL-17, interferon-γ), irritation, ischemia/hypoxia and trauma to produce TNFα which in turn enhances the production of a number of inflammatory factors mediating and modulating the inflammatory response, and also providing positive or negative feedback to TNFα. IL-1, for example, enhances the production of TNFα which increases the production of IL-1 whereas negative feedback is regulated through interleukin 10 (IL-10) (Tracey et al. 2008).

5.2 TNFα receptors

Two receptors that mediate the action of TNFα have been found, i.e. TNFR1 and TNFR2 (Hohmann et al. 1989, Brockhaus et al. 1990). The extracellular domains to which the ligand binds are cysteine-rich subdomains that are distinctive characteristics of the TNFα receptor gene family. Due to the different structures of their cytoplasmic domains, they activate different signal-transduction pathways (Dembic et al. 1990). TNFR1 is a type I transmembrane protein that exists as trimer and is mainly stored in inactive cells in the Golgi apparatus being released to the cell surface upon cell stimulation (Bradley 2008). In unstimulated receptors, the cytoplasmic domain is associated with a protein in cytoplasm called silencer of death domain (SODD) that has a role in preventing signalling of TNFR1. Binding of TNFα to TNFR1 and TNFR2 induces receptor

trimerization and recruitment of several signalling proteins to the cytoplasmic domains of the receptors. TNFR1 acts mainly as a pro-inflammatory mediator and triggers an immune response and inflammation, while TNFR2 has a primary role in stimulating the proliferation of T cells and in suppressing TNFα-mediated inflammatory responses. Both forms of TNFα receptors have been detected in synovial tissue and in the junction between cartilage and pannus (Deleuran et al. 1992, Westacott et al. 1994) localizing mainly in the lining layer, whereas TNFα is expressed most often in the deeper layer (Alsalameh et al. 1999).

Both receptors can be found also in soluble forms as a result of action of TACE (Bradley 2008) and they have been detected also in body fluids (Loetscher et al. 1990, Smith et al. 1990). Soluble TNFRs regulate at least in part the activity of TNFα since they can bind active TNFα (Cope et al. 1992, Choy and Panayi 2001).

The most important cellular response activated by TNFR signalling is activation of nuclear factor κB (NF-κB). The NF-κB family consists of five subunits that can exist in different homodimer and heterodimer forms to activate a wide range of target genes. In unstimulated cells, different dimers are bound to inhibitory proteins that ensure that they are unable to trigger gene transcription. In RA, activation of the NF-κB pathway results in expression of the genes involved in inflammation. In the classical pathway NF-κB activation can be induced by activation of TNFR1 leading to phosphorylation, ubiquitination and proteolysis of IκBs that in turn leads to release of NF-κB subunits that are able to translocate to the nucleus. (Brown et al. 2008, Simmonds and Foxwell 2008)

In most cases activation of TNFR1 receptor leads through TNFR-associated DD protein (TRADD) to K63 polyubiquitination of TNFR-associated factor 2 (TRAF2) and receptor interacting protein (RIP). Within minutes this receptor complex penetrates into the cell and TNFR1 is released from the TRADD-RIP-1-TRAF complex. The polyubiquitination chains associate with transforming growth factor-beta (TGFβ) -activated kinase (TAK) 1-binding protein 2 and 3 (TAB2 and TAB3), and activate the TAK kinase complex which in turn may activate IκB kinase (IKKβ) by phosphorylating it. In cytosol, IκB is bound to NF-κB to inactivate it. (Brown et al. 2008, Simmonds and Foxwell 2008)

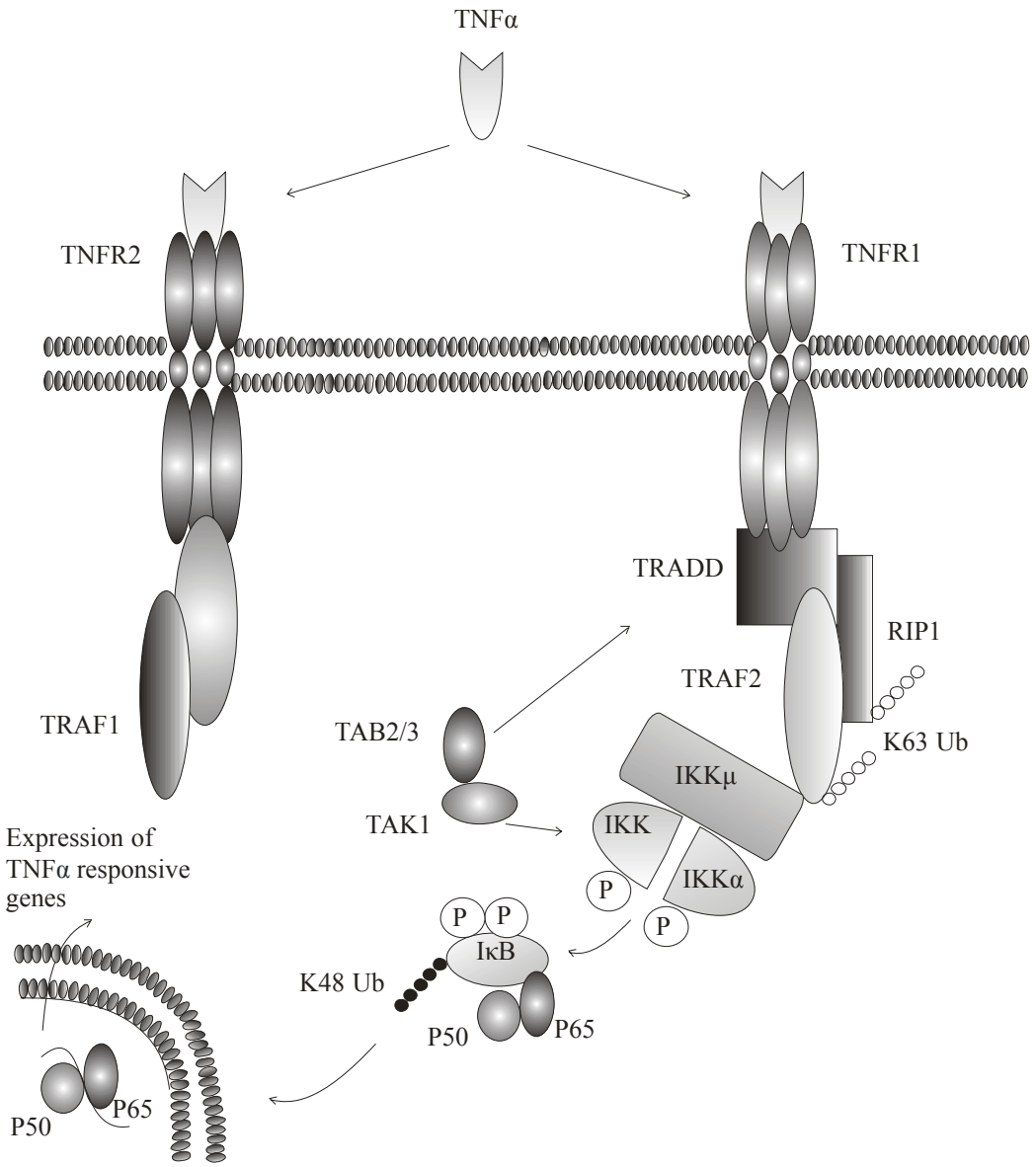

Figure 2. *Activation of TNFR1 and TNFR2 by TNFα. TNFR1 activation induces receptor trimerization and recruitment of the adapter protein TRADD that binds to a specific region of the cytoplasmic domain TNFR1. Ligand engagement of membrane receptor triggers K63 polyubiquitination of TRAF and RIP, and also recruits IKK to the receptor complex. This may also lead to conformational changes in the IKK complex. Degradation of IκBα releases the NF-κB heterodimers, which enter to the nucleus and regulate gene expression. IKK, IκB (inhibitor of kappa B) kinase; TAB, TAK1-binding protein; TAK, transforming growth factor-beta (TGF-beta)-activated kinase; TNFR, tumor necrosis factor alpha receptor; TRADD, TNFR associated DEATH domain protein; TRAF, TNFR-associated factor; RIP, receptor interacting protein.*

Activated IKKβ phosphorylates IκB (inhibitor of kappa B) leading to K48 polyubiquitination and to proteolysis. The released NF-κB migrates to the nucleus where it activates its target genes (Bradley 2008, Brown et al. 2008). (Figure 2)

Another signalling route is mediated via caspase-8 and caspase-3 activation; two enzymes that can cause apoptotic cell death. The apoptosis pathway is usually prevented by FADD-like IL-1β activation pathway (Ware 2005).

Activation of TNFR2 has been less extensively studied, but this receptor can also lead to the activation of NF-κB pathways. The receptor signal proceeds through TRAF (Ware 2005).

5.3 Effects of TNFα

TNFα regulates different inflammatory processes in RA and SpA as it is at the top of the cytokine cascade (Feldmann and Maini 2001) and the expression of synovial TNFα can be reduced by infliximab therapy and in that way the inflammatory response can be lessened (Ulfgren et al. 2000) In an animal model, dysregulated TNFα production led to chronic polyarthritis, which could be prevented by administration of an antibody against TNFα (Keffer et al. 1991). Furthermore in *Tnf*$^{-/-}$ mice, collagen induced arthritis develop only in part of exposed animals with milder symptoms and later time of onset than in wild type mice (Campbell et al. 2001).

As a result of the increased levels of TNFα, different pathologic processes are triggered (Figure 3) and aggravate inflammatory arthritis (Brennan and McInnes 2008). For example, as a result of increased TNFα expression in inflamed synovial tissue, endothelial cells become activated and adhesion molecules, like ICAM-1 and E-selectin are expressed in excess amounts. The adhesion molecules assist leukocyte infiltration into inflammatory tissue (Sweeney and Firestein 2004) and thus the leukocyte accumulation into inflammatory sites can be reduced by infliximab treatment (Tak et al. 1996). Different inflammatory cells are also activated by TNFα and they produce inflammatory cytokines, including IL-1 (Buchan et al. 1988) and IL-6 (Hirano et al. 1988). A reduction in the concentration of IL-6 in serum has been detected

after infliximab infusion in RA patients (Charles et al. 1999) and the level of an acute phase reactant, serum CRP is decreased (Elliott et al. 1993).

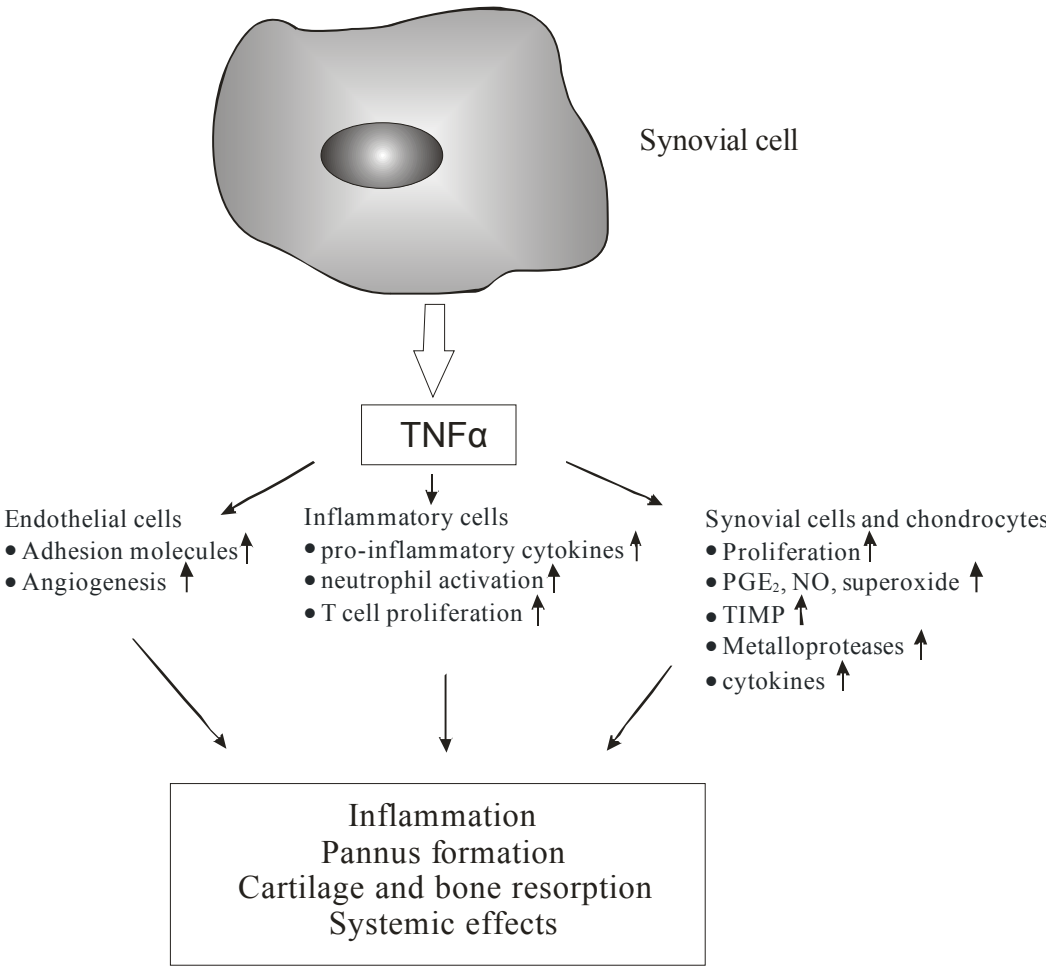

Figure 3. *Effects of tumor necrosis factor alpha (TNFα) in rheumatoid arthritis (RA). ↑, increase. PGE, prostaglandin E; NO, nitric oxide; TIMP, tissue inhibitor of metalloproteinases*

Rheumatic synovium contains a large number of T-cells (Firestein 2003). TNFα, in addition to IL-6 and IL-1 initiates differentiation of Th17 type lymphocytes which express IL-17, a pro-inflammatory cytokine that mediates synovitis and articular damage (Imboden 2009). Neutrophils are also found in rheumatic synovium and these cells are activated by TNFα which can be prevented by infliximab treatment (Pay et al. 2005). TNFα can activate transcription factor activator protein-1 (AP-1) in synoviocytes to produce metalloproteinases (Firestein 2003). In synovial cells and cartilage different

mediators are released after TNFα regulation, for example NO (Bingham 2002, Vuolteenaho et al. 2002) and this release can be modulated by anti-TNFα therapy (Vuolteenaho et al. 2002). It is known that TNFα increases synovial cell proliferation (Firestein 2003).

TNFα has a role in host defence against infections that has been confirmed by studies with TNFα receptor-deficient mice. Furthermore, an elevated risk of infections has been linked with anti-TNFα therapy (Furst et al. 2006). Resistance to bacterial infections, like *Mycobacterium* or *Listeria,* has been shown to be regulated by TNFα. The formation and maintenance of granulomas is influenced by TNFα (Roach et al. 2002, Wallis et al. 2005). However, the estimation of the involvement is complicated because of the fact that patients with RA seem to be at an increased risk for suffering infections (Mutru et al. 1985, Doran et al. 2002b, Doran et al. 2002c).

Patients with RA are in increased risk of developing lymphomas. Although TNFα antagonists have been associated with an elevated risk of malignancy, recent studies have indicated that drug treatment does not further increase that risk (Kaiser 2008). Atherosclerosis is linked to inflammation during all stages of the disease. Thus TNFα can modify the traditional risk factors for atherosclerosis, e.g. it promotes the development of dyslipidaemia and insulin resistance. Adhesion molecules are upregulated by TNFα leading eventually to fatty streak formation and the initiation of atherosclerosis. Finally inflammation can lead to the rupture of the plaque (Dixon and Symmons 2007).

In RA and other inflammatory diseases, like SpA and JIA, TNFα is the driving force for inflammation. Overexpression of TNFα leads to dysregulation of immune cells and cytokines and other inflammatory mediators that in turn induce pathological changes within the joints. TNFα also plays a pivotal role in inflammatory bowel diseases (e.g. Crohn's disease) and it has been shown to be upregulated in the intestine of patients with active disease (Panes et al. 2007).

5.4 TNFα antagonists in the treatment of rheumatoid arthritis and spondyloarthropathies

Despite the fact that traditional DMARDs provide many patients with a good clinical improvement and even remission, some patients are resistant to

DMARDs, also when given as a combination treatment. This phenomenon led to development of new drugs and the introduction of the first biological drugs in the treatment of RA directed against TNFα. At the moment, there are three different TNFα antagonists in clinical use, infliximab, etanercept and adalimumab and recently two other compounds in the group were introduced, i.e. TNFα monoclonal antibody golimumab and pegylated antibody certolizumab. They all have been found to be effective in the treatment in rheumatic and other inflammatory diseases.

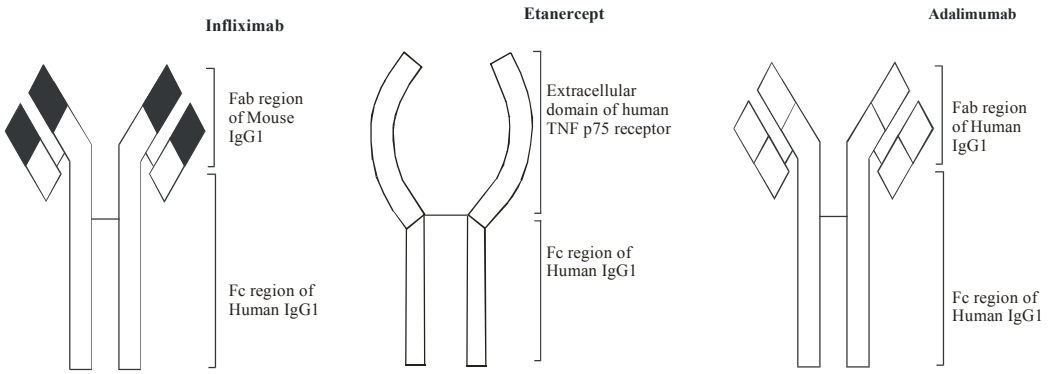

Figure 4. *Structure of the anti-tumor necrosis factor alpha (TNFα) antagonists investigated in the present study.*

5.4.1 Infliximab

Infliximab (Figure 4) is a chimeric monoclonal antibody which binds to against TNFα. It is composed of Fc region of a human IgG and a murine Fab part. In confirmation to *in vitro* and animal studies, early clinical data suggested that TNFα would be an important target for specific biological therapy in RA (Knight et al. 1993).

Infliximab in rheumatoid arthritis

Elliott et al. evaluated the safety and efficacy of a chimeric monoclonal antibody targeted to TNFα in patients with RA treated with a total dose of 20 mg/kg of the TNFα antagonist in an open phase I/II trial for 8 weeks. Fifteen patients received two infusions at a dose of 10 mg/kg at two weeks intervals and five patients received four infusions at a dose of 5 mg/kg on days 0, 4, 8 and 12. In addition to

clinical and laboratory improvements, the patients tolerated the treatment well. Since the preliminary results were so good, these workers were encouraged to continue further studies with the TNFα antagonist. (Elliott et al. 1993)

In a double-blind trial, 73 patients with active RA were randomized to have either a single infusion of 1 or 10 mg/kg of cA2 (infliximab) or placebo in addition to their oral glucocorticoid or DMARD treatment. After four weeks, the response rate at Paulus 20% criteria (Paulus et al. 1990) was 8% in placebo group, 44% in 1 mg/kg recipients, and 79% in 10 mg/kg recipients. The corresponding response rates at Paulus 50% criteria were 8%, 28% and 58%. Five infections and four injection related reactions did take place (Elliott et al.1994a).

The experience from previous studies had indicated that patients could experienc a relapse after a single infliximab infusion during follow-up. In order to examine the use of repeated infusions of cA2 (infliximab), eight patients were treated with two to four cycles which were scheduled by disease flare. Most cycles were administered within five weeks of relapse. Individual patients exhibited varying responses, but the median Paulus 20% response duration after treatment with 20 mg/kg in cycle two was 9 weeks. Adverse events included infections, infusion reactions and development of antinuclear antibodies. (Elliott et al. 1994b)

The efficacy, pharmacokinetics, immunogenicity, and safety of cA2 (infliximab) were studied in a multicenter study. A total of 101 RA patients from six different centers were randomized to seven groups. In three groups infliximab was administered at doses of 1, 3 or 10 mg/kg concomitantly with 7.5 mg/week of oral methotrexate, whereas in other three groups, the patients received 1, 3 or 10 mg/kg of infliximab without methotrexate. One group received methotrexate and placebo. The clinical response was evaluated by the Paulus 20% and 50% index (Paulus et al. 1990) after 26 weeks of follow-up. Anti-TNFα therapy given together with methotrexate evoked a better response than methotrexate alone. Four patients achieved complete remission and 12 patients achieved partial remission for at least eight consecutive weeks. In the placebo plus methotrexate group, the patients discontinued the treatment mainly due to lack of efficacy. Minor adverse events were more common in groups

receiving infliximab (83%) than methotrexate only (57%). Infusion reactions occurred in five patients during the infusion period and necessitated discontinuation of the treatment. One patient discontinued because of a rash after one week which appeared after the fourth infusion. Almost one of three (32%) patients receiving infliximab developed an infection requiring antimicrobial treatment as compared to 21% of the patients receiving placebo plus methotrexate. Finally, 8% of the cA2-treated patients developed anti-dsDNA antibodies and one patient suffered systemic lupus erythematosus (SLE). (Maini et al. 1998)

In a trial of 428 RA patients, infliximab at a dose 3 or 10 mg/kg or placebo was given intravenously at either four or eight week intervals. All patients had previously received continuous methotrexate for at least three months and at a stable dose for at least four weeks. An ACR50 response was achieved after 30 weeks treatment by between 26-31% of the patients depending on the infliximab dose and infusion intervals. The incidence of infections in patients receiving infliximab at the dose of 10 mg/kg in four weeks intervals was 73% as compared to 47% in patients receiving 3 mg/kg or 40% in placebo group. Three malignancies were diagnosed, all in patients receiving infliximab at 10 mg/kg, though the incidence was not greater than that of age and sex matched population. (Maini et al. 1999)

Patients from the above report were included also in the 54 weeks' follow-up study, when 79% of the patients were continuing with the infliximab and methotrexate treatment. Twelve per cent of patients in infliximab plus methotrexate group and 36% of the patients receiving methotrexate alone had discontinued therapy due to lack of efficacy. Although there were no significant differences in the frequency of infections, respiratory tract infections were more common in the groups receiving infliximab plus methotrexate compared to those receiving methotrexate alone. Also some serious infections were reported, such as urinary infections, sepsis, pneumonia and tuberculosis. Radiographic changes were retarded in infliximab plus methotrexate groups as compared to those receiving methotrexate alone. (Lipsky et al. 2000)

The results of the 24 months' follow-up of the above mentioned study were reported in a separate article. Infliximab plus methotrexate resulted in a greater

improvement than methotrexate alone. An ACR50 response was achieved by 20-36% of the patients in the infliximab group depending on the dose and infusion intervals, and but only by 6% in methotrexate group. In the infliximab plus methotrexate group, 55-68% of patients completed the study depending on the dose and infusion intervals, compared to only 16% in methotrexate group. Patients who received infliximab in addition to methotrexate suffered less progression in the structural damage than those treated with methotrexate plus placebo. The adverse events were very similar in all groups. (Maini et al. 2004)

In early RA, infliximab combined with methotrexate has been shown to confer better efficacy and also a superior antierosive benefit versus methotrexate alone (Breedveld et al. 2004, St Clair et al. 2004).

Infliximab in ankylosing spondylitis

Infliximab has proved effective and well tolerated in the treatment of AS (Brandt et al. 2000, Stone et al. 2001, Braun et al. 2002a, Braun et al. 2003, van der Heijde et al. 2005, Braun et al. 2006, Braun 2008) and also in other spondyloarthropathies (van den Bosch et al. 2002). The adverse events were similar to those observed in the treatment of RA. Radiographic progression was reduced in infliximab-treated patients when compared to conventionally treated AS patients (Baraliakos et al. 2005b). On the contrary, van der Heijde et al. did not observe any statistically significant difference in inhibition of radiographic progression in infliximab-treated patients compared to placebo-treated (van der Heijde et al. 2008b). However, inflammatory changes at the spine as measured by MRI were diminished by infliximab treatment (Braun et al. 2006).

Infliximab in juvenile idiopathic arthritis

In a non-randomised, prospective, open label study of 14 JIA patients, infliximab was effective and well tolerated. The study patients were treated with infliximab added to their previous DMARD treatment. In three patients, an infusion related reaction appeared, one patient developed symptoms and signs of macrophage activation syndrome and one girl became anti-dsDNA antibody positive and a previous alopecia reoccurred. One patient did not reach ACR Pedi50 and therefore infliximab treatment was discontinued. (Lahdenne et al. 2003)

In a pilot study, repeated infusions of infliximab were given at a dose of 3 mg/kg combined with methotrexate to 24 JIA patients (Gerloni et al. 2005). In their subsequent prospective study, patients were randomized to receive first infliximab 3 mg/kg or placebo for 14 weeks, after which all children received infliximab through week 44. Patients received infliximab at a dose of 3 mg/kg with methotrexate through week 44, or placebo plus methotrexate for 14 weeks followed by infliximab 6 mg/kg with concomitant methotrexate through week 44. A rapid clinical response was observed, but in the infliximab 3 mg/kg group there were more infections and these infections were more serious than in the 6 mg/kg or placebo groups. Four patients (three in 3 mg/kg and one in 6 mg/kg group) suffered a possible anaphylactic reaction. (Ruperto et al. 2007)

Twenty-one JIA patients with uveitis were treated with infliximab and the ophthalmological status improved after 24 months' treatment in nine (43%) patients in conjunction with the clinical articular improvement (Tynjälä et al. 2007).

In the retrospective study conducted by Tynjälä et al., 104 JIA patients with infliximab treatment were followed and the treatment survival at 12 months was 80% and declining at 24 months to 68%. The main reasons for discontinuation were inefficacy (20%), adverse events (22%) or inactive disease (16%). (Tynjälä et al. 2009)

5.4.2 Etanercept

A therapeutic response was noted to treatments achieving an elevated concentration on soluble TNFRs in serum and synovial fluid in RA since these receptors function as endogenous TNFα antagonists (Cope et al. 1992, Barrera et al. 1993, Chikanza et al. 1993, Roux-Lombard et al. 1993). Therefore a recombinant human TNFR P75-Fc fusion protein (TNFR:Fc, later known as etanercept) was developed and as expected it was found to neutralize TNFα (Mohler et al. 1993). The production of TNFR:Fc was achieved by combining DNA formed from two linked single DNAs where one DNA sequence encoded the soluble portion of human TNFR p75 and the other DNA part encoded for the

Fc portion of a human IgG1 molecule (Figure 4). When TNFR:Fc was added to active TNFα, the total biological activity of TNFα was reduced.

Etanercept in rheumatoid arthritis

The safety and pharmacokinetics of recombinant human tumor necrosis factor receptor (p80) fusion protein (rhTNFR:Fc) was evaluated in a four week trial with 22 RA patients. Sixteen patients had a single intravenous loading dose followed by subcutaneous maintenance injections twice weekly for one month. The patients were subdivided into four different dose groups and in each group three patients received drug and one patient received placebo. After four weeks, three additional patients received the highest dose and three additional patients received the lowest dose in an open label study to obtain more safety data. There were no serious adverse events. Mild injection site reactions did occur in four patients. (Moreland et al. 1996)

The study was continued on the basis of these positive results to encompass a multicenter, double-blind trial to evaluate the safety and efficacy of TNFR:Fc (etanercept). A total of 180 patients with refractory RA were randomly assigned to receive one of three doses of TNFR:Fc (0.25, 2 or 16 mg per square meter of body-surface area), or placebo, twice a week for three months. The disease activity reduced significantly and the therapeutic effect was dose-related, the highest dose of TNFR:Fc resulted in the greatest improvement in the number of swollen and tender joints. The most common adverse events were mild injection-site reactions and mild upper respiratory tract symptoms. No dose limiting toxic effects appeared and only one patient had to terminate treatment because of an injection site reaction. No antibodies to TNFR:Fc were detected in serum. (Moreland et al. 1997)

A randomized, double-blind, placebo-controlled trial with blinded joint assessors evaluated 234 patients with active RA despite treatment with different DMARDs. Patients were treated with placebo or 10 or 25 mg of etanercept subcutaneously twice a week for six months. At 6 months, 59% of the patients receiving 25 mg of etanercept and 11% of the placebo recipients reached an ACR20 response, and ACR50 response was achieved by 40% and 5% of the patients, respectively. The most common adverse events were mild injection site

reactions, which were suffered by 49% of the patients receiving 25 mg etanercept, of whom only one patient discontinued the treatment. (Moreland et al. 1999)

In a study of 89 RA patients, the combination of methotrexate and etanercept proved effective and well tolerated. Patients were randomized to have either etanercept 25 mg or placebo subcutaneously twice a week while continuing to receive methotrexate. Injection site reactions were more common in patients treated with the combination than in those receiving methotrexate alone. The most common adverse events encountered by patients were infections, and in all groups there were some patients with lymphocytopenia (Weinblatt et al. 1999).

The safety and efficacy of etanercept in 628 RA patients was evaluated an a study which had a median treatment time of 25 months. The study included patients from the three above studies who had failed to respond to their previous DMARD treatment and had received at least one dose of etanercept. Nine per cent of patients discontinued due to lack of efficacy and seven per cent due to an adverse event. A serious infection that required hospitalization or intravenous antibiotics had occurred in 43 patients and eight malignancies were reported. (Moreland et al. 2001)

Etanercept treatment has also been studied in early RA. Bathon et al. treated 632 patients with early RA with subcutaneous etanercept twice a week at a dose of 10 or 25 mg as compared to oral methotrexate once a week at a mean dose of methotrexate 19 mg per week. At 12 months 80-85% of the patients were still receiving the treatment depending on the dose compared to 79% of methotrexate patients. A more slowly radiographic progression appeared in patients receiving 25 mg of etanercept than in patients receiving methotrexate. The number of patients with infections was similar in all groups. (Bathon et al. 2000)

In the trial of the combination therapy with methotrexate and etanercept was significantly better than either drug alone. After a 52 week follow-up, an ACR50 response was achieved by 69% of patients in the combination group as compared with 43% and 48% in the methotrexate and etanercept groups, respectively. The number of reported infections was similar in all groups (Klareskog et al. 2004).

Etanercept in ankylosing spondylitis

In the treatment of AS, etanercept was found to be effective and well tolerated as compared to placebo (Calin et al. 2004, Brandt et al. 2005), but also serious adverse events appeared. One patient developed Crohn's disease which was thought to be related to etanercept treatment (Brandt et al. 2005). Radiographic changes were not significantly retarded in etanercept-treated patients compared to placebo group receiving standard anti-inflammatory drug therapy (van der Heijde et al. 2008a). An MRI scan revealed that the inflammatory findings in spine were reduced at both the 24 weeks' and 24 months' follow-up inspections (Baraliakos et al. 2005a, Rudwaleit et al. 2005). However, some of the patients did not experience a satisfying reduction in spinal inflammation at the 24 months' survey (Baraliakos et al. 2005a).

Etanercept in juvenile idiopathic arthritis

Today, etanercept is established in the treatment of JIA. Lovell et al. first evaluated the safety and efficacy of etanercept in patients with polyarticular JIA who had failed to respond to methotrexate treatment. Initially, 43 girls and 26 boys with a mean of 6 years' disease history were enrolled in an open-label study. All patients received etanercept 0.4 mg/kg subcutaneously twice a week for up to three months in the open-label phase and 51 of the 69 patients responded to treatment and were entered into the double-blind study. After randomization, 51 patients received either placebo or etanercept 0.4 mg/kg subcutaneously for a maximum of seven months. After the whole follow-up period (seven months), out of the total 51 who started the trial 6/26 in placebo and 18/25 in etanercept group completed the whole study. The most common adverse events were infections and injection site reactions (Lovell et al. 2000). In the long-term evaluation of the safety and efficacy, study patients were further followed-up for 24 months, with infections being the the most common adverse events (Lovell et al. 2003). Recently the eight years' data was published, where 34% of the patients were still continuing with the treatment. The main reasons for discontinuation of etanercept treatment were lack of efficacy and adverse events, 12% and 7%, respectively (Lovell et al. 2008a).

Severe adverse events were reported in 12 patients in a study with 61 JIA patients during years 1999 to 2001. These adverse effects included neurologic or psychiatric disorders, retrobulbar optic neuropathy, major weight gain, severe infection, cutaneous vasculitis with systemic symptoms, hemorrhagic diarrhea, uveitis flare and pancytopania. After discontinuation of etanercept, all adverse events disappeared (Quartier et al. 2003).

In an open-label (previously partially described) study, 10 polyarticular JIA patients received etanercept. ACR Paediatric 50 was achieved at 3, 6 and 12 months time by 90, 89 and 89%, respectively. One patient discontinued due to lack of efficacy (Lahdenne et al. 2003)

Twenty-four JIA patients with uveitis were treated with etanercept and in five (21%) patients the ophthalmological status improved after 24 months' treatment along with clinical articular improvement (Tynjälä et al. 2007).

In a retrospective study of 105 JIA patients on etanercept treatment, drug survival at 12 and 24 months was 83% and 68%, respectively. The main reasons for discontinuation were lack of efficacy (28%), adverse event (7%) or inactive disease (10%) (Tynjälä et al. 2009).

5.4.3 Adalimumab

The safety and efficacy of fully human anti-TNFα monoclonal antibody (Figure 4) D2E7 (adalimumab) has been tested in different experimental systems. The ability of D2E7 to prevent arthritis was demonstrated in a transgenic mouse line that expressed 3'-modified human tumor necrosis factor (hTNFα) transgenes. These mice develop arthritis which resembles RA both clinically and histologically. When the transgenic mice were treated with a monoclonal antibody against human TNFα, this resulted in the complete prevention of arthritis (Keffer et al. 1991).

Adalimumab in rheumatoid arthritis

Since the preliminary results of adalimumab (D2E7) in the treatment of RA were promising, more clinical trials were performed (Kempeni 1999). For example,

patients with active RA treated with a single dose of adalimumab experienced a rapid clinical response (Barrera et al. 2001).

In a randomized, double blind, placebo controlled trial, 120 patients with active RA were treated with single ascending doses of adalimumab from 0.5 up to 10 mg/kg. Safety, pharmacokinetics and efficacy were determined over a four week period. The effects were seen during the first week, even a mere after 24 hours. The maximum effect was reached after 1-2 week's treatment. Single doses of adalimumab were well tolerated. (den Broeder et al. 2002)

When adalimumab was compared to methotrexate in the treatment of RA, the patients on adalimumab responded better than those on methotrexate. The most common adverse events were common cold, rash and flu-like symptoms. (Barrera et al. 2002)

In the multicenter trial (ARMADA), a total of 271 RA patients were treated with adalimumab at a dose of 20, 40 or 80 mg subcutaneously or with placebo every other week in addition to their standard methotrexate treatment. After 24 weeks of treatment, an ACR20 response was achieved by 48%, 67% and 66% of patients in 20, 40 and 80 mg groups, respectively. In placebo plus methotrexate group ACR20 response was achieved by 15%. Infections, usually in the upper respiratory tract, and injection site reactions were the most common adverse events. In all, seven patients had to withdraw from the study because they had experienced an adverse event. (Weinblatt et al. 2003)

In the extended ARMADA trial with a four year follow-up, RA patients with adalimumab treatment with concomitant methotrexate were reported to experience a sustained clinical response. The incidence of serious infections had not increased significantly at four years when compared to the six months' results. (Weinblatt et al. 2006)

In a 26 week clinical study, 60 patients were randomized to receive adalimumab at a dose of 0.25, 0.5, 1, 3 or 5 mg/kg or placebo with or without methotrexate. ACR50 improvement was achieved in 11-44% of the patients on adalimumab, depending of the dose, but none of the 15 patients receiving placebo achieved ACR50. The most common adverse events were headache, nausea, rhinitis, increased cough and dizziness. Two serious adverse events

appeared in one individual, who developed septic arthritis and soft tissue infection. (Weisman et al. 2003)

In a 24 week study, a total of 636 RA patients were randomized to receive adalimumab 40 mg or placebo every other week while they continued their standard DMARD treatment. In this trial, nearly 29% of the adalimumab-treated and 11% of the placebo-treated patients achieved ACR50 and there were no statistically significant differences in the rates of serious or other infections between the groups. (Furst et al. 2003)

In early RA, the efficacy and safety of combination therapy with adalimumab and methotrexate were compared to methotrexate or adalimumab monotherapy in 799 RA patients in a 24 months' intervention (PREMIER). The study patients were methotrexate naive and had a disease duration of less than three years. The ACR50 response was achieved by 62% of the patients receiving adalimumab plus methotrexate at 12 months and by 59% at 24 months. In patients receiving adalimumab alone, 41% and 37% achieved ACR50 at 12 and 24 months, respectively. In patients treated with methotrexate alone, bone erosions were more common than in those receiving adalimumab in combination with methotrexate. Serious infections appeared more often in the adalimumab plus methotrexate group than in patients receiving adalimumab alone. (Breedveld et al. 2006)

In a multicenter trial, 619 RA patients on methotrexate treatment were randomized to receive adalimumab at doses of 20 or 40 mg per week subcutaneously, or placebo. Adalimumab was found to be antierosive and also to induce a better clinical improvement compared to placebo after 52 weeks of treatment. (Keystone et al. 2004)

Adalimumab in ankylosing spondylitis

Adalimumab has also been shown to be anti-inflammatory and well tolerated in AS. The most frequent adverse events associated with the treatment were upper respiratory tract infections, headache and diarrhea. In addition, injection site reactions appeared. (Haibel et al. 2006, van der Heijde et al. 2006, Lambert et al. 2007, van der Heijde et al. 2009) The progress of radiographic changes was slower in adalimumab-treated patients as compared to placebo or

methotrexate-treated patients (Keystone et al. 2004, Emery et al. 2009). In contrast, van der Heijde et al. did not observe any inhibition of radiographic progression in AS patients treated with adalimumab (van der Heijde et al. 2009).

Adalimumab in juvenile idiopathic arthritis

Recently Lovell et al. published promising results on the treatment of polyarticular JIA with adalimumab concluding that it represented a good treatment option (Lovell et al. 2008b). That study included 171 JIA patients from 4 to 17 years of age with active disease who were treated in open-label phase either with adalimumab in addition to their previous methotrexate treatment (n=85) or with adalimumab as monotherapy (n=86). During the open-label phase, all patients were receiving adalimumab at a dose of 24 mg /m^2 subcutaneously every other week for 16 weeks. From the 86 patients without methotrexate 64 (74%) and from the 85 patients receiving methotrexate 80 (94%) experienced an ACR Pedi30 response at week 16. All of the patients who had achieved ACR Pedi30 response were enrolled into the double-blind phase and were randomized to four different groups to receive subcutaneous adalimumab or placebo every other week for 32 weeks with or without methotrexate. At week 48, an ACR Pedi30 response was achieved in 57% of the adalimumab-treated patients without methotrexate and in 63% of the patients receiving methotrexate in addition to adalimumab. Comparable values in placebo-treated patients were 32% and 38%. The most frequently reported adverse events were infections and injection-site reactions. (Lovell et al. 2008b)

In a retrospective study, 20 JIA patients with JIA and chronic uveitis treated with adalimumab were evaluated with respect to the clinical response. In 14 of the 20 patients disease activity in joints was observed in addition to uveitis. Adalimumab was effective, i.e. 6/14 (43%) of the patients had inactive arthritis after the follow-up period and in 7/20 (35%) of the patients, the symptoms of uveitis improved. (Tynjälä et al. 2008)

Aims of the study

The purpose of the present study was to investigate anti-TNFα therapy in the treatment of RA, SpA and JIA in everyday practice which was according to the national guidelines by focusing on the following detailed aims:

1. to study the effects of infliximab on cytokine concentrations, and on myeloperoxidase enzyme and soluble adhesion molecule levels in patients with JIA (I)
2. to investigate treatment continuation and discontinuation (drug survival) during anti-TNFα therapy in patients with RA or SpA (II, III, IV)
3. to identify the reasons for discontinuation of anti-TNFα therapy in patients with RA or SpA (II, III, IV)
4. to investigate in more detail the adverse events which caused discontinuation of anti-TNFα therapy in patients with RA or SpA (II, III, IV)

Materials and methods

1 Patients

1.1 Study I

The study included eight patients with JIA (Table 8) from the previous study of Lahdenne et al. (Lahdenne et al. 2003). They fulfilled the ILAR classification criteria of JIA (Petty et al. 1998) and were treated with infliximab. Five of the patients were girls and three boys, with a mean age of 10 years (range 5-14 years). The mean age at onset of JIA was 5 years (range 3-8 years). Before the infliximab treatment was started, the patients had suffered from an active disease for at least one year and their disease was refractory to standard treatments which included different combinations of methotrexate, prednisolone, cyclosporine A, sulfasalazine, and / or hydroxychloroquine and i.e. glucocorticoid injections. All patients were receiving NSAIDs as a symptomatic treatment.

Table 8. *Patient characteristics in study I.*

Patient	Sex (F / M)	Age (years)	Diagnosis	Disease duration (years)	HLAB27	Rheumatoid Factor	Antinuclear Antibodies	Iritis
1	F	9	Extended oligoarthritis	3	negative	negative	positive	yes
2	F	12	Polyarthritis	10	negative	negative	negative	yes
3	M	13	Extended oligoarthritis	8	positive	negative	positive	yes
4	F	7	Polyarthritis	5	negative	negative	positive	yes
5	M	9	Polyarthritis	1	negative	negative	negative	no
6	F	5	Extended oligoarthritis	3	positive	negative	negative	no
7	M	10	Polyarthritis	3	negative	negative	negative	yes
8	F	12	Polyarthritis	10	negative	negative	negative	yes

1.2 Studies II, III and IV

The study population included 200 consecutive RA and SpA patients (Figure 5), treated in the Department of Internal Medicine, Section of Rheumatology of the Tampere University Hospital, Finland, who commenced anti-TNFα therapy as their first biologic treatment for active RA or SpA during the years 1999 to 2005. RA group included also adult patients with JIA.

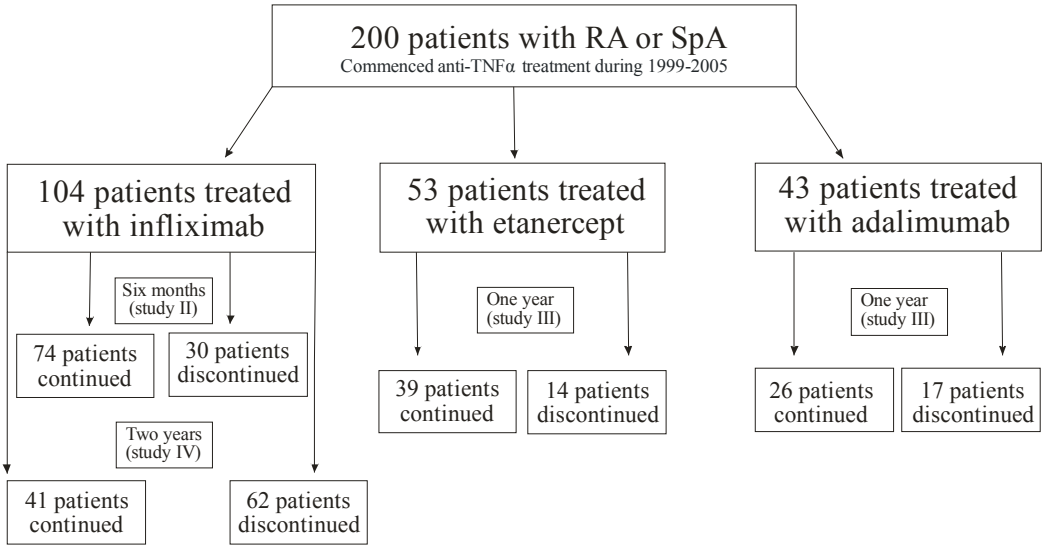

Figure 5. *Patients in studies II, III and IV.*

Studies II and IV consisted of 104 patients with severe RA or SpA who were started infliximab treatment. Sixty-two per cent of the patients (64 patients) were female, and at the beginning of infliximab treatment the mean age was 45 (range 18-75) years and the mean duration of the disease was 12 (range 0.8-52) years (Table 9). Sixty-two (60%) patients had RA and nearly 60% of them (37 patients) had seropositive RA, one fourth (16 patients) had seronegative RA and about 15% (10 patients) had JIA (Table 10). Forty-two (40%) of the patients had SpA and about 40% (18 patients) of them had AS and nearly 20% (8 patients) PsA (Table 10). Seronegative oligoarthritis, enteropathic arthritis, ReA and sacroiliitis were represented in minor part (Table 10).

Table 9. *Characteristics of patients commenced anti-tumor necrosis factor alpha (TNFα) therapy.*

	infliximab group	etanercept group	adalimumab group
	(n = 104)	(n = 53)	(n = 43)
Age, years (range)	45 (18-75)	44 (18-75)	52 (17-74)
Female (%)	62 %	58 %	72 %
Disease duration, years (range)	12 (0.8-52)	10 (1-36)	16 (1-45)
Number of concomitant DMARDs			
0 (%)	5 %	6 %	7 %
1 (%)	37 %	22 %	32 %
2 (%)	29 %	36 %	26 %
3 or more (%)	29 %	36 %	35 %
Glucocorticoid intake (%)	91 %	81 %	93 %
Glucocorticoid dose (mean; mg/day)	10	6.8	7.4

DMARD,disease modifying antirheumatic drug.

Table 10. *Infliximab-treated patients (n=104) according to the diagnosis.*

Diagnosis	n
RA	62
Seropositive RA	37
Seronegative RA	15
JIA	10
SpA	42
Ankylosing spondylitis	18
Psoriatic arthritis	8
Seronegative oligoarthritis	5
Enteropathic arthritis*	4
Reactive arthritis	4
Sacroiliitis	3

RA, rheumatoid arthritis; JIA, juvenile idiopathic arthirits;
*SpA, spondyloarthropathy; *Crohn's disease and ulcerative colitis*

Most of the patients (95%) were treated with one or more concomitant DMARDs and 91% received low dose oral glucocorticoids in accordance to the national recommendations for infliximab treatment (Table 9).

Study III included 53 patients treated with etanercept and 43 patients with adalimumab. At the onset of the treatment, the mean age of the patients receiving etanercept was 44 (range 18-75) years, 58% (31 patients) were female and the mean disease duration was 10 (range 1-36) years (Table 9).

Table 11. *Etanercept-treated patients (n=53) according to their diagnosis.*

Diagnosis	n
RA	31
Seropositive RA	21
Seronegative RA	5
JIA	5
SpA	22
Ankylosing spondylitis	10
Psoriatic arthritis	5
Seronegative oligoarthritis	4
Sacroiliitis	2
Reactive arthritis	1

RA, rheumatoid arthritis; SpA, spondyloarthropathy;
JIA, juvenile idiopathic arthritis

Thirty-one (58%) patients had rheumatoid arthritis including seropositive RA in 21 (68%), seronegative RA in 5 (16%) and JIA in 5 patients (16%) (Table 11). Twenty-two (42%) of the 53 patients had SpA including AS in 10 (45%) and PsA in 5 patients (23%). Seronegative oligoarthritis, reactive arthritis and sacroiliitis were represented to a minor degree (Table 11).

Forty-three patients with RA or SpA started adalimumab as their first biological treatment (Table 9). The mean age at the beginning of the treatment was 52 (range 17-74) years, 72% of the patients were female and the mean duration of the disease was 16 (range 1-45) years (Table 9). Most of the patients (93%) were using at least one concomitant DMARD and 93% of them received also oral glucocorticoids (Table 9). Forty patients (93%) had RA and three-quarters of them had seropositive disease. Fifteen per cent of the RA patients had seronegative RA and 10% had JIA. Three patients (7%) had SpA (Table 12).

Table 12. *Adalimumab-treated patients (n=43) according to their diagnosis.*

Diagnosis	n
RA	40
Seropositive RA	30
Seronegative RA	6
JIA	4
SpA	3
Seronegative oligoarthritis	3

RA, rheumatoid arthritis; SpA, spondyloarthropathy;
JIA, juvenile idiopathic arthritis

2 Methods and measurements

2.1 Methods in study I

Infliximab (3-4 mg/kg) was given intravenously at weeks 0, 2, 6 and thereafter at approximately six weeks intervals to the JIA patients (Table 8). Clinical response was assessed and blood samples for cytokine and adhesion molecule assays were collected before the first infusion and after 6, 12 and 24 weeks treatment. The clinical response was assessed by an experienced paediatric rheumatologist before the first infliximab infusion and at weeks 6, 12 and 24 just before the scheduled infliximab infusion. Four clinical parameters were registered: number of active joints, number of swollen joints, ESR and CRP. The study was approved by the ethical committee of Helsinki University Hospital. Patients and/or parents provided written informed consent before the commencement of the study.

Reagents and laboratory methods in study I

Serum samples were stored at -70° C until analysed. Myeloperoxidase (MPO) was measured by radioimmunoassay (MPO-RIA Pharmacia & Upjohn, Uppsala, Sweden). Cytokines were measured by enzyme-immunoassay using the following reagents: IL-6 and IL-10 (PeliPair ^{TM}, Sanquin Reagents, Amsterdam, The Netherlands), IL-1Ra, IL-1β, sTNFR1, sTNFR2 and TNFα (Quantikine^{TM}

Immunoassay, R&D Systems, Minneapolis, MN, USA) and IL-18 (MBL ELISA, Medical & Biological Laboratories CO LTD, Nagoya, Japan). Soluble forms of adhesion molecules ICAM-1 and E-selectin (i.e. sICAM-1 and sE-selectin) were measured by reagents from HyCult Biotechnology (Uden, The Netherlands).

Statistics: The results are expressed as mean ± standard error of mean (SEM). Repeated measures analysis of variance followed by Bonferroni multiple comparisons test was used in the statistical analysis. P-values less than 0.05 were normally considered significant.

2.2 Methods in studies II, III and IV

Indications for the use of anti-TNFα therapy were based on national recommendations (Rheumatoid arthritis: Current Care Guidelines 2009). The criteria to start anti-TNFα therapy treatment for RA was that the patient had been suffering from continuously active disease (at least six swollen and tender joints, and additionally the duration of morning stiffness ≥ 45 min and/or ESR ≥ 30 mmHg and/or serum CRP ≥ 28 mg/l despite treatments with combinations of traditional DMARDs including methotrexate and glucocorticoids.

The criteria to start anti-TNFα therapy for the treatment of AS included 1) inefficiency of at least two NSAIDs for at least three months, 2) sulfasalazine (or methotrexate if sulfasalazine was contraindicated) or possibly other DMARDs have been ineffective, and 3) the patient had an active disease based on BASDAI (≥ 4 cm) and on clinical grounds (acute sacroiliitis, elevated acute phase reactants, MRI findings).

In the other spondyloarthropathies like PsA or IBD associated arthritides, there was no defined criteria for biologicals available, but the decision was made on clinical grounds by the treating rheumatologist based on the severity of oligo/polyarthritis and inflammatory axial disease, and when applicable, criteria for the treatment of RA and AS were used.

In this observational study, patients were treated individually by their treating rheumatologist and visiting schedule was individually followed. Patient records of all patients who started infliximab, etanercept or adalimumab were able to

retrieve and examined afterwards. The study did not include any invasive operations and was approved by the Medical Director of the Tampere University Hospital.

In studies II and IV, infliximab infusions were given on weeks 0, 2, 6 and every 8 weeks thereafter at a dose of 3 mg/kg. Based on the clinical response, the dose of infliximab could be elevated or lowered, or the infusion intervals shortened or lengthened. In study III, etanercept was given subcutaneously at a dose of 25 mg twice a week and adalimumab by a dose of 40 mg every other week subcutaneously. Anti-TNFα therapy was combined usually with methotrexate and often with other DMARDs (mostly sulfasalazine or hydroxychloroquine) and low-dose prednisolone. The clinical response was carefully registered by an experienced rheumatologist at outpatient visits. In RA, the clinical evaluation was based on ACR response criteria (Felson et al. 1995) including number of swollen and tender joints, the physician's assessment of disease activity (VAS 0-10 cm), patient's assessment of general health (VAS), pain (VAS) and HAQ, and markers of acute phase activity (ESR and CRP). A treatment response less than ACR50 was regarded as ineffective. In AS and other SpA, the clinical response was evaluated by using BASDAI and BASFI indexes, and the treatment was regarded as ineffective if the decline in the BASDAI index was less than 50% or 2 cm.

Summary of the results

1 Circulating cytokines and soluble adhesion molecules in patients with juvenile idiopathic arthritis during infliximab treatment (I)

The study included eight patients with JIA who all responded favourably to infliximab treatment. Clinical parameters were found to improve already during the first six weeks of treatment (Table 13), and the good clinical response was maintained up to the end of the 24 weeks of treatment. We investigated changes in the concentrations of inflammatory cytokines and other inflammatory factors along with clinical improvement.

Table 13. *Effects of infliximab treatment on clinical parameters and inflammatory factors during infliximab treatment in patients (n=8) with juvenile idiopathic arthritis (JIA).*

	Duration of the treatment (weeks)			
Parameter	0	6	12	24
Active joints	16.3 ± 4.4	3.6 ± 1.2**	3.4 ± 1.2**	4.4 ± 2.3**
Swollen joints	13.3 ± 4.8	2.1 ± 1.0*	3.9 ± 1.2	2.4 ± 1.4*
CRP (mg/l)	31 ± 7.8	8.4 ± 3.1**	9.3 ± 3.5**	6.6 ± 1.5***
ESR (mm/h)	38.9 ± 5.5	17.4 ± 2.8***	15.8 ± 2.8***	18.1 ± 4.4***
IL-6 (pg/ml)	14.6 ± 3.4	7.6 ± 2.0*	7.2 ± 1.3*	8.4 ± 2.2
IL-18 (pg/ml)	292 ± 44.3	262 ± 24.3	282 ± 28.8	285 ± 34.0
MPO (ng/ml)	584 ± 121	373 ± 55.7*	368 ± 41.1*	373 ± 66.1*
IL-10 (pg/ml)	2.3 ± 0.6	2.3 ± 0.5	2.1 ± 0.4	2.2 ± 0.4
IL-1Ra (pg/ml)	793 ± 303	459 ± 104	546 ± 88.1	573 ± 84.5
sTNFR1 (pg/ml)	1381 ± 127	1137 ± 69.6*	1242 ± 94.7	1118 ± 94.6**
sTNFR2 (pg/ml)	2251 ± 285	1971 ± 170	2045 ± 234	2092 ± 238
TNFα (pg/ml)	20.8 ± 6.0	28.7 ± 10.9	28.1 ± 8.4	51.3 ± 11.1
sICAM-1 (ng/ml)	145 ± 5.4	129 ± 8.6***	135 ± 7.7**	134 ± 7.1**
sE-Selectin (ng/ml)	68.2 ± 6.5	57.0 ± 6.0**	63.1 ± 7.0	62.6 ± 7.0

*Mean ± SEM, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ compared to the baseline.*
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; MPO, myeloperoxidase; sTNFR, soluble tumor necrosis factor α receptor; TNFα, tumor necrosis factor α; sICAM-1 and sE-selectin, soluble adhesion molecules. Reprinted with permission from: Levälampi et al.2008, Scand J Rheumatol 36:189-193. © Taylor&Francis, modified.

During 24 weeks follow-up CRP decreased from 31 ± 7.8 to 6.6 ± 1.5 mg/l and ESR from 38.9 ± 5.5 to 18.1 ± 4.4 mm/h.

Concentrations of IL-6 in serum were reduced during infliximab treatment. After six weeks' treatment with infliximab, the IL-6 levels were about 50% lower than before the commencement of the treatment and remained at the reduced level during the 24 weeks' treatment period (Figure 6A). MPO levels in the serum samples from JIA patients declined significantly during infliximab treatment. After six weeks treatment, MPO levels were about 35% lower than before the treatment, and remained at that lower level along with the good clinical response during the 24 weeks treatment period (Figure 6B).

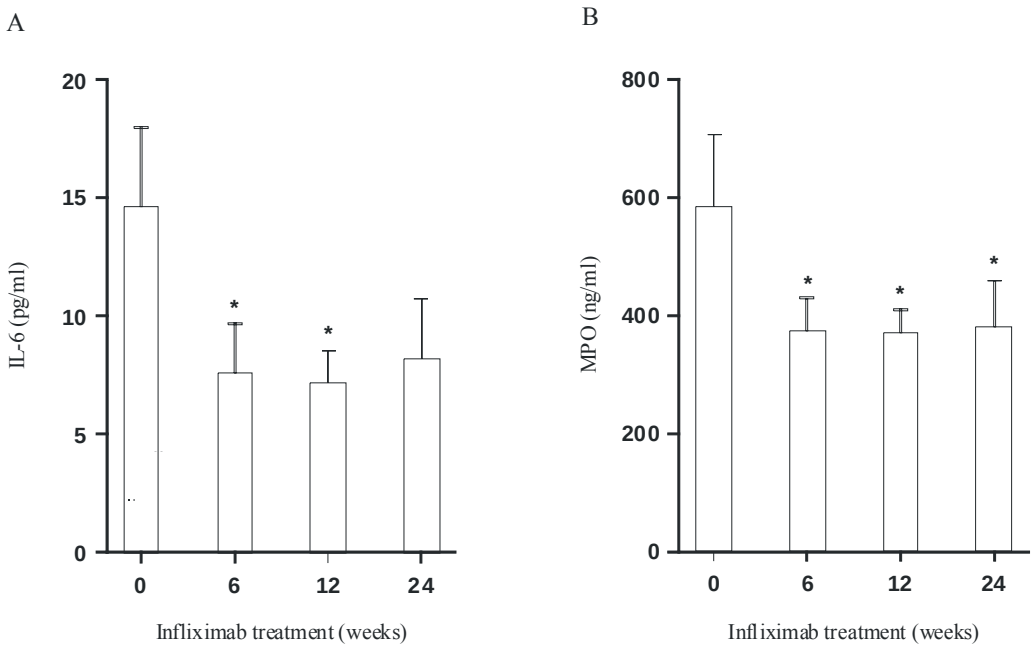

Figure 6. *Levels of interleukin 6 (IL-6) (A) and myeloperoxidase (MPO) (B) during infliximab treatment in patients with juvenile idiopathic arthritis. Mean ± SEM, n=8. *p<0.05. (Reprinted with permission from: Levälampi et al. 2008, Scand J Rheumatol 36:189-193. © Taylor&Francis)*

sE-selectin and sICAM-1 were detectable in serum, and their levels became reduced to some extent during infliximab treatment. The maximal mean decreases were 16% and 10% in sE-selectin and sICAM-1 concentrations, respectively; these reductions were statistically significant (Table 13).

No significant changes were found in IL-18 levels during infliximab treatment (Table 13), and the IL-1β concentrations were below the detection

limit of the enzyme-immunoassay used (detection limit of the assay was 2 pg/ml).

The mean levels of IL-1Ra reduced during the study but the change was not statistically significant, and the mean level of IL-10 remained at its low constant level throughout the study (Table 13). The soluble TNFR1 concentrations in serum declined during the treatment, the mean concentration at the beginning was 1381 pg/ml and at the end of the study it was 1118 pg/ml ($p<0.01$). The mean levels of sTNFR2 concentrations decreased to some extent but the change was not statistically significant (Table 13). Moreover, TNFα concentration in serum samples increased in six out of the eight patients, and the mean increase during 6 months' treatment was about 150% (Table 13).

2 Drug survival with anti-TNFα treatment in patients with rheumatoid arthritis or spondyloarthropathy (II, III and IV)

Two hundred RA and SpA patients were treated with anti-TNFα therapy as their first biological treatment in Tampere University Hospital during the years 1999-2005. In all, 104 of them were treated with infliximab, 53 with etanercept and 43 with adalimumab. Drug survival was determined after six, 12 and 24 months in infliximab-treated patients, and after 12 months in the etanercept and adalimumab-treated patients.

After six months' infliximab treatment (Table 14), 71% of the patients (74 / 104 patients) had achieved at least a 50% treatment response and were continuing with the treatment. Infliximab treatment had been discontinued in 30 patients. Adverse events and lack of efficacy were the most common reasons for discontinuation of treatment. After six months of follow-up, the continuing rate in patients with RA was two thirds (43 / 63 patients, 68%) and slightly better (31 / 41 patients, 76%) in SpA patients (Table 14).

At the 12 months' assessment (Table 15) of the 104 patients, 53% (55 / 104 patients) were continuing and 46% (48 / 104 patients) had discontinued infliximab treatment.

Table 14. *Characteristics of the infliximab-treated patients at the beginning and after six months of the treatment.*

	At the beginning	After six months of infliximab treatment					
	Started	Continuing	Discontinued				
	All (n = 104)	All (n = 74)	All (n = 30)	Remission (n = 7)	Inadequate response (n = 8)	Adverse event (n = 13)	Other reason (n = 2)
Age, years, mean (range)	45 (18-75)	45 (18-76)	47 (22-75)	36 (22-59)	47 (28-56)	31 (28-75)	47 (24-71)
Female (%)	62 %	57 %	73 %	86 %	50 %	77 %	100 %
Disease duration, years, mean (range)	12 (0.8-52)	13 (1-30)	12 (1-53)	10 (1-26)	6 (2-13)	17 (2-53)	16 (4-29)
Number of concomitant DMARDs							
0 (%)	5 %	3 %	20 %	0 %	13 %	23 %	50 %
1 (%)	37 %	41 %	33 %	100 %	25 %	23 %	0 %
2 (%)	29 %	28 %	30 %	0 %	25 %	39 %	50 %
3 or more (%)	29 %	28 %	17 %	0 %	37 %	15 %	0 %
Glucocorticoid intake (%)	91 %	82 %	80 %	86 %	100 %	77 %	100 %
Glucocorticoid dose, mean (mg/day)	10	5.7	8.7	4.6	16.3	6.1	16.9

DMARD, disease modifying antirheumatic drug.
Reprinted with permission from: Levälampi et el. 2008, Scand J Rheumatol 37:6-12. © Taylor&Francis, modified.

Table 15. *Characteristics of the infliximab-treated patients at the beginning and after 12 months of the treatment.*

	At the beginning	After 12 months of infliximab treatment					
	Started	Continuing	Discontinued				
	All (n = 104)	All (n = 55)	All (n = 48)	Remission (n = 8)	Inadequate response (n = 17)	Adverse event (n = 17)	Other reason (n = 6)
Age, years, mean (range)	45 (18-75)	44 (18-76)	48 (19-76)	36 (19-59)	43 (28-56)	52 (28-75)	56 (24-76)
Female (%)	62 %	49 %	76 %	100 %	53 %	82 %	83 %
Disease duration, years, mean (range)	12 (0.8-52)	13 (1-30)	12 (1-53)	12 (1-26)	10 (2-23)	15 (2-53)	16 (4-29)
Number of concomitant DMARDs							
0 (%)	5 %	0 %	14 %	0 %	6 %	6 %	33.3 %
1 (%)	37 %	42 %	34 %	62 %	36 %	35 %	33.3 %
2 (%)	29 %	28 %	38 %	12 %	29 %	41 %	33.3 %
3 or more (%)	29 %	30 %	14 %	35 %	29 %	18 %	0 %
Glucocorticoid intake (%)	91 %	81 %	86 %	63 %	94 %	94 %	100 %
Glucocorticoid dose, mean (mg/day)	10	5.6	8.2	4.1	12.2	7.4	9.4

DMARD, disease modifying antirheumatic drug. One patient was lost to follow-up (moved to another district).

Table 16. *Characteristics of the infliximab-treated patients at the beginning and after 24 months of the treatment.*

	At the beginning	After 24 months of infliximab treatment					
	Started	Continuing	Discontinued				
	All (n = 104)	All (n = 41)	All (n = 62)	Remission (n = 7)	Inadequate response (n = 23)	Adverse event (n = 25)	Other reason (n = 7)
Age, years, mean (range)	45 (18-75)	44 (22-74)	48 (22-76)	44 (22-59)	43 (29-62)	51 (23-75)	55 (24-71)
Female (%)	62 %	49 %	71 %	86 %	57 %	76 %	86 %
Disease duration, years, mean (range)	12 (0.8-52)	15 (3-31)	13 (1-53)	12 (1-26)	10 (2-23)	15 (2-53)	15 (3-29)
Number of concomitant DMARDs							
0 (%)	5 %	7 %	13 %	0 %	4 %	20 %	28 %
1 (%)	37 %	37 %	35 %	57 %	35 %	32 %	29 %
2 (%)	29 %	19 %	31 %	29 %	26 %	36 %	29 %
3 or more (%)	29 %	37 %	21 %	14 %	35 %	12 %	14 %
Glucocorticoid intake (%)	91 %	78 %	84 %	71 %	91 %	88 %	100 %
Glucocorticoid dose, mean (mg/day)	10	4.8	7.8	3.9	10.4	9.1	9.5

DMARD, disease modifying antirheumatic drug. One patient was lost to follow-up (moved to another district).
Reprinted with permission from: Levälampi et el. 2009, Rheum Int, in press. © Springer-Verlag Berlin, modified.

The patients (n=104) were included in another analysis after 24 months' treatment. At that time point, 40% of the patients (41 / 104 patients) had sustained at least a 50% treatment response and were continuing infliximab treatment (Table 16). In 60% of the patients (62 / 104 patients), lack of efficacy, an adverse event or some other reason had led to discontinuation of the infliximab treatment during the 24 months of follow-up. Thirty-seven per cent of the RA patients (23 / 62 patients) and 44% of the SpA patients (18 / 42 patients) were still continuing infliximab after 24 months of treatment.

The use of glucocorticoids was most prevalent at the beginning of infliximab treatment. The number of patients on glucocorticoid treatment declined during six months and also during 24 months of infliximab treatment, from 91% to 82% (6 months) and further to 78% (24 months). In addition, the mean equivalent dose of prednisolone had been reduced from 10 mg to 5.7 mg (6 months), to 5.6 mg (12 months) and to 4.8 mg/day (24 months). When examined at six months and 12 months, the number of patients without concomitant DMARD's had decreased (from 5 to 3 and 0%, respectively) but at 24 months the percentage had increased back to seven. The same phenomenon was seen in the number of patients having three or more DMARDs. At 24 months, the number of patients with three or more DMARDs had increased (from 29% to 37%) being previously (at six months and 12 months) approximately at the initial level (Tables 14-16).

Etanercept (Table 17) and adalimumab (Table 18) treatments were sustained in 74% (39 / 53 patients) and 60% of the patients (26 / 43 patients) at the 12 months' follow-up, respectively. Twenty-six per cent of etanercept-treated patients (14 / 53 patients) and 40% (17 / 43 patients) of those treated with adalimumab did not achieve a 50% improvement and discontinued the treatment at some point during the 12 months of follow-up. The most common reasons for discontinuation were inadequate responses and adverse events. The comparable data of 12 months' in infliximab treatment is given in Table 19.

Table 17. *Characteristics of etanercept-treated patients at the beginning and after 12 months of the treatment.*

	At the beginning	After 12 months of etanercept treatment	
	(n = 53)	Continuing (n = 39)	Discontinued (n = 14)
Age, years, mean (range)	44 (18-75)	44 (19-76)	44 (26-61)
Female (%)	58 %	53 %	67 %
Disease duration, years, mean (range)	10 (1-36)	13 (3-37)	7 (1-22)
Number of concomitant DMARDs			
0 (%)	6 %	25 %	17 %
1 (%)	22 %	47 %	17 %
2 (%)	36 %	20 %	50 %
3 or more (%)	36 %	8 %	17 %
Glucocorticoid intake (%)	81 %	52 %	83 %
Glucocorticoid dose, mean (mg/day)	6.8	2.9	5.4

DMARD, disease modifying antirheumatic drug.

Reprinted with permission from: Levälampi et el. 2008, Rheumatol Int 28:261-9. © Springer-Verlag Berlin Heidelberg, modified

Table 18. *Characteristics of adalimumab-treated patients at the beginning and after 12 months of the treatment.*

	At the beginning	After 12 months of adalimumab treatment	
	(n = 43)	Continuing (n = 26)	Discontinued (n = 17)
Age, years, mean (range)	52 (17-74)	50 (24-70)	56(17-74)
Female (%)	72 %	73 %	76 %
Disease duration, years, mean (range)	16 (1-45)	16 (2-34)	17 (1-45)
Number of concomitant DMARDs			
0 (%)	7 %	8 %	18 %
1 (%)	32 %	58 %	41 %
2 (%)	26 %	31 %	12 %
3 or more (%)	35 %	4 %	29 %
Glucocorticoid intake (%)	93 %	73 %	100 %
Glucocorticoid dose, mean (mg/day)	7.4	3.6	8.1

DMARD, disease modifying antirheumatic drug.

Reprinted with permission from: Levälampi et el. 2008, Rheumatol Int 28:261-269. © Springer-Verlag Berlin Heidelberg, modified.

Table 19. *Characteristics of infliximab-treated patients at the beginning and after 12 months of treatment.*

	At the beginning	After 12 months of infliximab treatment	
	Started (n = 104)	Continuing (n = 54)	Discontinued (n = 50)
Age, years, mean (range)	45 (18-75)	44 (18-76)	48 (19-76)
Female (%)	62 %	49 %	76 %
Disease duration, years, mean (range)	12 (0.8-52)	13 (1-30)	12 (1-53)
Number of concomitant DMARDs			
0 (%)	5 %	0 %	14 %
1 (%)	37 %	42 %	34 %
2 (%)	29 %	28 %	38 %
3 or more (%)	29 %	30 %	14 %
Glucocorticoid intake (%)	91 %	81 %	86 %
Glucocorticoid dose, mean (mg/day)	10	5.6	8.2

DMARD, disease modifying antirheumatic drug

In those patients continuing the etanercept or adalimumab treatment at 12 months, the proportion of the patients on oral glucocorticoids diminished from 81% to 52% in the etanercept group (Table 17) and from 93% to 73% in the adalimumab group (Table 18). The mean glucocorticoid dose declined by 52% among continuers in the etanercept group. In addition, the number of concomitant DMARDs was reduced in conjunction with successful etanercept treatment (Table 17). During 12 months of adalimumab treatment the proportion of the patients with concomitant DMARD treatment decreased as well (Table 18).

3 Reasons for discontinuation of the anti-TNFα treatment in patients with rheumatoid arthritis or spondyloarthropathy (II, III and IV)

At the six months' time point, 30 patients (29%) had discontinued infliximab treatment; twenty-three per cent of them (7 / 30 patients) due to remission and 27% (8 / 30 patients) due to lack of efficacy. Due to adverse events infliximab treatment had been discontinued in 43% of the patients (13 / 30 patients). One female patient discontinued due to intention to conceive and one patient died due to cerebral infarction during the follow-up. The results are summarized in Table 20. Forty-six per cent of the adverse events that were responsible for discontinuation of the treatment were infections (6 / 13 patients) and 38% (5 / 13 patients) were hypersensitivity reactions. One patient discontinued the infliximab treatment because of drug related leukopenia and one patient because of elevated serum aminotransferase activities (Table 23).

Table 20. *Reasons to discontinue infliximab treatment.*

	Six months' follow-up		12 months' follow-up		24 months' follow-up	
Reason	Number	%	Number	%	Number	%
Remission	7	23	8	22	7	11
Lack of efficacy	8	27	17	36	23	37
Adverse event	13	43	17	34	25	40
Other reason	2	7	6	8	7	11
Total	30	100	48	100	62	100

By the 12 months' follow-up, a total of 46% of the patients (48 / 104 patients) had discontinued infliximab treatment with the reasons shown in Table 20. Eight patients achieved remission, 17 had an inadequate response, 17 patients experienced an adverse event and 6 patients had other reason.

During 24 months of follow-up, 60% of the patients (62/104 patients) had discontinued infliximab treatment with the main reasons being adverse event (25 cases) (Figure 7) and lack of efficacy (23 cases), 7 patients were in remission, and 7 patients had other reason. One patient moved to another district and was lost to follow-up (Table 20).

Fourteen (26%) etanercept-treated patients discontinued the treatment during 12 months (Table 21), in 50% this was due to an inadequate response. Six patients discontinued the treatment because of a severe adverse event. Cumulative occurrence of adverse events over time is shown in Figure 7. One patient discontinued due to intention to conceive.

Table 21. *Reasons to discontinue etanercept treatment during the 12 months of follow-up*

Reason	Number	%
Lack of efficacy	7	50
Adverse event	6	43
Other reason	1	7
Total	14	100

Reprinted with permission from: Levälampi et al. 2008, Rheumatol Int 28:261-9. © Springer-Verlag Berlin

Adalimumab treatment was discontinued in 17 (40%) patients during the 12 months' follow-up (Table 22). Four (23%) patients did not achieve a 50% improvement and thus treatment was discontinued due to poor response. In 11

(65%) patients adverse events were responsible for discontinuation of the treatment, the time when the adverse event occurred is seen in Figure 7. One patient discontinued of his own will and one patient due to changes in chest radiology, not related to adalimumab treatment.

Table 22. *Reasons to discontinue adalimumab treatment during the 12 months of follow-up.*

Reason	Number	%
Lack of efficacy	4	23
Adverse event	11	65
Other reason	2	12
Total	17	100

Reprinted with permission from: Levälampi et al. 2008, Rheumatol Int 28:261-9. © Springer-Verlag Berlin

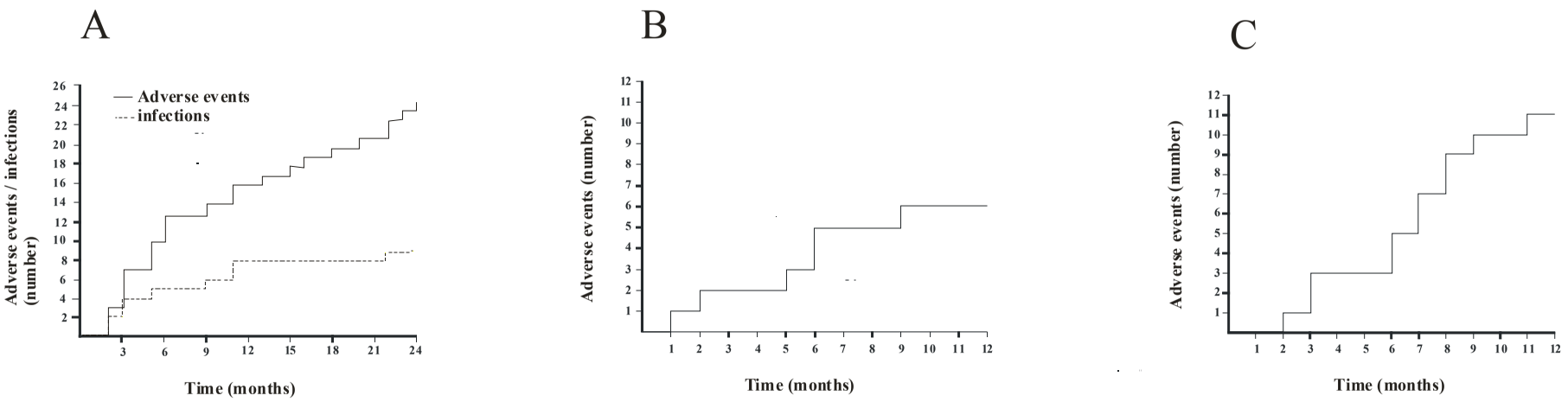

Figure 7. *Cumulative occurence of adverse events which caused discontinuation of the infliximab (A), etanercept (B) and adalimumab (C) treatment over time. Reprinted with permission from: Levälampi et el. 2008, Rheumatol Int 28:261-9. © Springer-Verlag Berlin Heidelberg, modified.*

4 Adverse events which caused discontinuation of the anti-TNFα treatment in patients with rheumatoid arthritis or spondyloarthropathy (II, III and IV)

4.1 Infections

During six months of follow-up six out of 104 patients treated with infliximab discontinued the treatment because they suffered a severe infection (II). Three of the infections were pneumonias of bacterial etiology and two of those pneumonias had typical clinical signs and symptoms and radiological findings. The third patient was diagnosed as having pulmonary tuberculosis. The three other infections were septic arthritis of ankle, gluteal abscess and generalized infection (Table 23). One of the patients restarted infliximab treatment later.

During the 24 months' follow-up, nine (ten) infliximab-treated patients were diagnosed to have an infection that compelled the discontinuation of infliximab treatment (IV). Four of the infections appeared after the first six months. Two out of those four infections were pneumonias, one patient had a recurrent urinary tract infections and one patient was diagnosed to have a septic arthritis (Table 24).

Table 23. *Adverse events which caused to discontinuation of infliximab treatment during six months' treatment.*

Classification	Nr	Diagnosis	Age	Sex	Disease duration (years)	DMARD's	Time of adverse event	Adverse event
Infection	1	Seropositive rheumatoid arthritis	49	F	6	MTX 10 mg/wk CyA 200 mg/day SSZ 2000 mg/day	After 3rd infusion	Pulmonary tuberculosis with mediastinum lymph nodes, diagnosed by biopsy.
	2	Seronegative rheumatoid arthritis	51	F	7	PRED 10 mg/day MTX 25 mg/wk	After 4th infusion	Infection (CRP 145 mg/ml), with unknown focus.
	3	Ankylosing spondylitis	53	M	6	PRED 10 mg/day MTX 25 mg/wk CyA 200 mg/day	After 4th infusion	Gluteal abscess.
	4	Seropositive rheumatoid arthritis	58	F	26	PRED 15 mg/day ATM 50 mg/6wk HCQ 300mg/day	After 2nd infusion	Septic arthritis of right ancle joint.
	5	Ankylosing spondylitis	50	M	12	SSZ 2000 mg/day	After 4th infusion	Pneumopericarditis.
	6	Seropositive rheumatoid arthritis	71	F	12	PRED 10 mg/day AF 9 mg / day	After 2nd infusion	Pneumonia.
Hypersensitivity reaction	1	Seronegative rheumatoid arthritis	28	F	15		During 4th infusion	Infusion reaction (rash), DMARDs stopped previously because of mild pharyngitis.
	2	Juvenile idiopathic arthritis	31	F	30	PRED5 mg/day CyA 100 mg/day SSZ 2000 mg/day AF 3 mg/day	During 4th infusion	Infusion reaction (dyspnea, rash and itching).
	3	Seronegative rheumatoid arthritis	40	M	2	PRED 5 mg/day MTX 10 mg/wk SSZ 2000 mg/day	During 4th infusion	Infusion reaction (rash).
	4	Psoriatic arthropathy	73	F	15	PRED 10 mg/day	After 4th infusion	Delayd infusion reaction (rash, dyspnea), developed two days after infusion.
	5	Seropositive rheumatoid arthritis	75	F	53	PRED 5 mg/day CyA 100 mg/day SSZ 2000 mg/day	During 5th infusio	Infusion reaction (hoarseness, dyspnoea, rash).
Other adverse event	1	Seronegative rheumatoid arthritis	36	F	19	PRED 5 mg/day CyA 100 mg/day SSZ 2000 mg/day	After 4th infusion	Elevation of ALT (alanine aminotransferase) 125-142 IU/l.
	2	Enteropathic arthropathy	58	F	22	PRED 5 mg/day SSZ 1000 mg/day	After 4th infusion	Cytopenia/neutropenia (1.4×10^9/l).

DMARD, disease modifying antirheumatic drug; AF, auranofin; ATM, aurothiomalate; CyA, cyclosporine A; HCQ, hydroxychloroquine; MTX, methotrexate; PRED, prednisolone; SSZ, sulfasalazine.Reprinted with permission from: Levälampi et al.2007, Scand J Rheumatol 37:6-12, modified.

Table 24. *Adverse events which caused discontinuation of infliximab treatment during 24 months' follow-up.*

Classification	Nr	Diagnosis	Age (years)	Sex	Disease duration (years)	DMARDs	Time of adverse event (months)	Adverse event
Hypersensitivity reaction	1	Seropositive rheumatoid arthritis	23	F	2	PRED 5 mg/day	22	Infusion reaction (pain and swelling of throat)
	2	Seronegative rheumatoid arthritis	28	F	15		6	Infusion reaction (rash), DMARDs stopped previously because of mild pharyngitis
	3	Juvenile idiopathic arthritis	31	F	30	PRED 5 mg/day CyA 100 mg/day SSZ 2000 mg/day AF 3 mg/day	3	Infusion reaction (dyspnoea, rash and itching)
	4	Enteropathic arthropathy	31	M	6	PRED 7,5 mg/day CyA 300 mg/day SSZ 3000 mg/day	18	Infusion reaction (headache, dyspnea and rash)
	5	Ankylosing spondylitis	35	M	7	MTX 5 mg/wk	13	Infusion reaction (dyspnea, swelling of throat and erythema of face)
	6	Seropositive rheumatoid arthritis	37	F	21	PRED 7,5 mg/day MTX 22,5 mg/wk	23	Delayed infusion reaction (itching and rash), developed four days after infusion
	7	Seronegative rheumatoid arthritis	40	M	2	PRED 5 mg/day MTX 10 mg/wk SSZ 2000 mg/day	3	Infusion reaction (rash in upper body)
	8	Seronegative rheumatoid arthritis	47	F	15	PRED 15 mg/day MTX 20 mg/wk SSZ 2000 mg/day	15	Infusion reaction (rash and itching)
	9	Seropositive rheumatoid arthritis	50	F	7	PRED 10 mg/day AZA 50 mg/day	20	Delayed infusion reaction (rash, itching and edema of face), developed few days after infusion
	10	Seropositive rheumatoid arthritis	52	F	6	PRED 5 mg/day CyA 150 mg/day SSZ 3000 mg/day HCQ 214 mg/day	5	Infusion reaction (dyspnea, rash and cough)
	11	Seropositive rheumatoid arthritis	54	F	11	PRED 10 mg/day MTX 20 mg/wk	1.5	Infusion reaction (malaise, chills and rash)
	12	Seropositive rheumatoid arthritis	73	F	25	MTX 5 mg/wk	15.5	Infusion reaction (rash and itching in the hand)
	13	Psoriatic arthropathy	73	F	15	PRED 10 mg/day	5.5	Delayed infusion reaction (rash, dyspnoea), developed two days after infusion
	14	Seropositive rheumatoid arthritis	75	F	53	PRED 5 mg/day CyA 100 mg/day SSZ 2000 mg/day	6	Infusion reaction (hoarseness, dyspnoea, rash)

Table 24 continues

Classification	Nr	Diagnosis	Age (years)	Sex	Disease duration (years)	DMARDs	Time of adverse event (months)	Adverse event
Infection	1	Seronegative oligoarthritis	43	F	19	PRED 5 mg/day MTX 25 mg/wk HCQ 257 mg/day	11	Septic arthritis of right knee joint
	2	Seropositive rheumatoid arthritis	49	F	6	MTX 10 mg/wk CyA 200 mg/day SSZ 2000 mg/day	1.5	Pulmonary tuberculosis with mediastinum lymph nodes, diagnosed by biopsy
	3	Seronegative rheumatoid arthritis	51	F	7	PRED 10 mg/day MTX 25 mg/wk	5	Infection (CRP 145 mg/ml) with unknown focus
	4	Ankylosing spondylitis	54	M	7	PRED 15 mg/day MTX 25 mg/wk SSZ 2000 mg/day	11	Pneumonia
	5	Ankylosing spondylitis	57	M	15	PRED 7,5 mg/day SSZ 2000 mg/day HCQ 300mg/day	22	Pneumonia
	6	Seropositive rheumatoid arthritis	58	F	26	PRED 15 mg/day ATM 50 mg/6wk HCQ 300mg/day	3	Septic arthritis of right ankle joint
	7	Ankylosing spondylitis	50	M	12	SSZ 2000 mg/day	3	Pneumopericarditis
	8	Seropositive rheumatoid arthritis	71	F	12	PRED 10 mg/day AF 9 mg / day	2	Pneumonia
	9	Seropositive rheumatoid arthritis	75	F	16	PRED 5 mg/day LEF 20 mg/every other day	9	Recurrent urinary tract infections
Other reason	1	Seropositive rheumatoid arthritis	44	F	15	PRED 10 mg/day CyA 150 mg/day HCQ 214 mg/day	24	Recurrent cytopenia / neutropenia (0.85-l.1 x 10^9/l)
	2	Enteropathic arthropathy	58	F	22	PRED 5 mg/day SSZ 1000 mg/day	5	Cytopenia / neutropenia (1.4 x 10^9/l)

DMARD, disease modifying antirheumatic drug; AF, auranofin; ATM, aurothiomalate; AZA, azathioprine; CyA, cyclosporine A; HCQ, hydroxychloroquine; MTX, methotrexate; PRED, prednisolone; SSZ, sulphasalazine.

During 12 months of etanercept treatment, one patient suffered a severe herpes infection which caused discontinuation of the treatment (Table 25).

Table 25. *Adverse events which caused discontinuation of etanercept treatment during 12 months' treatment.*

Classification	Nr	Diagnosis	Age (years)	Sex	Disease duration (years)	DMARDs	Time of adverse event (months)	Adverse event
Infection	1	Juvenile idiopathic arthritis	26	M	19	PRED 5 mg/day MTX 20 mg/week HCQ 300 mg/day	5	Recurrent generalized herpes
Injection reaction	1	Seropositive rheumatoid arthritis	34	F	3	PRED 7,5 mg/day	1	Redness, itching and irritation of the injection site
	2	Seronegative oligoarthritis	43	F	7	PRED 5 mg/day MTX 25 mg/week SSZ 2000 mg/day	1.5	Tingle and numbness of lower limbs, congestion of throat and headache
	3	Seronegative rheumatoid arthritis	43	F	14	PRED 20 mg/day/ LEF 150 mg/day HCQ 300 mg/day	6	Vesicles in mouth and genitals and itchiness of skin
Other adverse event	1	Seropositive rheumatoid arthritis	61	F	4	PRED 2.5mg/day MTX 25 mg/week SSZ 2000 mg/day HCQ 300 mg/day	9	Mucous adenocarcinoma of ovary with abdominal metastasis
	2	Sacroiliitis	37	F	1	MTX 20 mg/week SSZ 2000 mg/day	6	Leukopenia: leukocytes 3.1 x 10^9/l and polymorphonuclear leukocytes 1.16 x 10^9/l

DMARD, disease modifying antirheumatic drug; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; PRED, prednisolone; SSZ, sulfasalazine. Reprinted with permission from: Levälampi et el. 2008, Rheumatol Int 28:261-269. © Springer-Verlag Berlin Heidelberg, modified.

From all 11 adverse events that caused discontinuation of adalimumab treatment during the first 12 months of follow-up, six were infections (Table 26). Three of the six infections were recurrent (urinary tract, maxillary sinusitis and dermatitis) and two patients suffered persistent infections, one patient had an infectious ulcer in the toe and one patient *Herpes Zoste*r infection. One patient developed tinea of the palms.

Table 26. *Adverse events which caused discontinuation of adalimumab treatment during 12 months' treatment.*

Classification	Nr	Diagnosis	Age (years)	Sex	Disease duration (years)	DMARDs	Time of adverse event (months)	Adverse event
Infection	1	Seropositive rheumatoid arthritis	49	M	14	PRED 10 mg/day MTX 25 mg/week	8	Recurrent infections (sinusitis)
	2	Seronegative rheumatoid arthritis	54	F	9	PRED 10 mg/day	11	Eczema of the hands with vesicles, diagnosed by dermatologist as tinea
	3	Seropositive rheumatoid arthritis	54	F	15	PRED 5 mg/day MTX 25 mg/week SSZ 2000 mg/day	6	Herpes Zoster infection in the left part of the upper body
	4	Seropositive rheumatoid arthritis	59	F	29	PRED 5 mg/day	7	Recurrent infections (urinary tract infections)
	5	Seropositive rheumatoid arthritis	61	F	5	PRED 5 mg/day LEF 20 mg/day	6	Recurrent infections (dermatitis and urinary tract infection with fever)
	6	Seropositive rheumatoid arthritis	64	M	11	PRED 5 mg/day LEF 20 mg/day SSZ 2000 mg/day HCQ 300 mg/day	3	Infectious ulcer in the toe
Injection reaction	1	Seronegative rheumatoid arthritis	53	F	7	PRED 15 mg/day MTX 15 mg/week SSZ 2000 mg/day HCQ 300 mg/day	8	Local injection reaction
	2	Seropositive rheumatoid arthritis	67	F	45	PRED 7,5 mg/day HCQ 300 mg/day	2	Purple eczema of lower limbs
	3	Seropositive rheumatoid arthritis	74	F	13	PRED 12,5 mg/day LEF 20 mg/day	3	Malaise, tingling and numbness after 4th injection, after 5th injection intense headache
Other adverse event	1	Seropositive rheumatoid arthritis	33	F	10	PRED 7,5 mg/day MTX 25 mg/week HCQ 257 mg/day	7	Suspicion of mild SLE: rash, elevated DNA-antibodies (ad 297 titer) and decreased complement levels (C3 0,45 g/l & C4 0,04 g/l)
	2	Seropositive rheumatoid arthritis	61	F	20	PRED 5 mg/day	9	Insomnia and intense sweating, but also irregular injections

DMARD, disease modifying antirheumatic drug; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; PRED, prednisolone; SSZ, sulfasalazine. Reprinted with permission from: Levälampi et el. 2008, Rheumatol Int 28:261-9. © Springer-Verlag Berlin Heidelberg, modified.

4.2 Hypersensitivity reactions / Injection site reactions

Five of the 13 adverse events that required discontinuation of infliximab treatment in the first six months were hypersensitivity reactions (Table 23) with rash with or without dyspnoea as the main symptoms. Fourteen of the 25 adverse events in the infliximab-treated patients who discontinued infliximab during 24 months were hypersensitivity reactions (Table 24).

Three injection site reactions occurred during the 12 months after the initiation of etanercept treatment. Two patients experienced local injection site reactions and one patient suffered systemic symptoms (congestion of throat, headache and tingling in the lower limbs) (Table 25).

Three patients on adalimumab treatment developed injection site reactions which caused discontinuation of the treatment. One patient had a local injection site reaction, one patient developed a skin reaction in the legs diagnosed as purpura, and one patient suffered malaise and intense headache (Table 26).

4.3 Other adverse events which caused discontinuation of the treatment

Two patients on infliximab treatment developed neutropenia after five and 24 months' treatment, respectively, which normalized after discontinuation of infliximab (Table 24). One patient had elevation of transaminases, but it relieved after discontinuation of infliximab.

In the etanercept-treated group, one patient developed leukopenia after six months that disappeared after discontinuation of etanercept. Another patient had mucous adenocarcinoma of the ovary (Table 25).

Adalimumab treatment was discontinued in two patients for some other reason than infection or injection site reaction. One patient experienced intense sweating and insomnia. One patient discontinued treatment due to a suspicion of SLE with rash after seven months of treatment, and she also displayed elevated serum DNA-antibodies and lowered levels of complement components C3 and C4 (Table 26).

Discussion

1 General discussion

TNFα antagonists have established their position in the treatment of RA, SpA and JIA next to the traditional DMARDs. Their therapeutic effects are based on their ability to neutralise excess TNFα by binding to TNFα either as an antibody or a receptor analogue. TNFα holds a central position in the cytokine cascade, regulating either directly or indirectly the expression of a number of inflammatory factors. Therefore the blockade of this single cytokine, TNFα, can result in a significant anti-inflammatory and antierosive effect in a considerable number of patients with severe arthritis (Feldmann and Maini 2001).

The present study was an observational study on consecutive patients with refractory and active disease who were treated with TNFα antagonists on clinical grounds, and not a randomized clinical study in which patient selection had been planned beforehand. In addition, the conclusion on which of the TNFα antagonists would be used varied depending on the clinical decision of the rheumatologist, the availability of the medication and also on the economical situation of the patient. In Finland, medication for the patient is practically free if it is given in hospital, as infliximab infusions. On the other hand, etanercept and adalimumab treatments, which are dosed by the patients themselves, are not free but patients have to purchase them in pharmacies and pay a significant proportion of the costs of these expensive pharmaceuticals themselves.

When examining the patient records, the diagnoses and other information were collected as registered by the treating rheumatologist. In the records of two patients with diagnosis of RA, we noticed that they had suffered their symptoms already in their youth, but they had not diagnosed as having JIA. When diseases symptoms begin before the age of 16, an exact diagnosis might be delayed because of unclear symptoms and instead of JIA the patient would be diagnosed

as suffering from RA. This phenomenon is well-known and was present also in the present study concerning at least two patients.

ACR criteria and BASDAI and BASFI indexes are widely used as indicators for evaluating the clinical response in randomized clinical trials in RA and AS patients. They would also be useful tools for rheumatologists in their daily work as ways of evaluating a patient's clinical condition, if these parameters were measured and calculated in each visit. In the present study, the main focus was on studying drug survival and indicators of clinical response were not measured exactly, but according to the national guidelines, anti-TNFα therapy is continued only in those patients who achieve at least ACR50 response or a reduction in BASDAI of more than 50% or 2 cm.

Because of the nature of the present study with its heterogenous patient population, three different anti-TNFα antagonist molecules, different treatment periods, and lack of consistent inclusion / exclusion criteria it is not possible to make a direct comparison of the efficacy and safety of the three anti-TNFα antagonists. On the other hand, analysis of the patient records offers data of the outcomes of anti-TNFα treatment in everyday practice.

2 Inflammatory mediators during infliximab treatment in patients with juvenile idiopathic arthritis

The levels of pro-inflammatory cytokines are higher in the active phase compared to the inactive phase of inflammation, and this has also been observed in JIA patients (Rooney et al. 1995, Mangge and Schauenstein 1998, Yilmaz et al. 2001, Ou et al. 2002). In the present study, we measured the levels of circulating cytokines and soluble adhesion molecules in patients with active JIA who were refractory to standard treatments, but responded favourably to infliximab.

IL-6 is a proinflammatory cytokine which has an important role in joint inflammation (Wong et al. 2003). In the present study, infliximab treatment reduced the circulating IL-6 levels by about 50% when measured after six weeks of treatment, and the effect was maintained up to the end of the 24 weeks'

follow-up. Infliximab treatment has previously been shown to reduce circulating IL-6 levels in patients with RA (Charles et al. 1999, Ohshima et al. 1999, Marotte et al. 2005).

MPO is released by activated neutrophils in chronic inflammation and it acts as a cytotoxic effector molecule, and as an immunoregulatory molecule that induces the production of numerous proinflammatory cytokines in macrophages (Lefkowitz and Lefkowitz 2001). MPO levels in serum samples have been reported to be elevated in patients with RA (Torsteinsdottir et al. 1999). In the present study, serum MPO levels in JIA patients were reduced by about 35% during the six weeks of treatment with infliximab, and remained at that lower level in conjunction with the good clinical response over the 24 weeks' treatment. Fejoo et al. reported recently that infliximab reduces concentrations of MPO in inflammatory joint disease (Fejoo 2009). The results emphasize the significance of neutrophils in JIA (Tak et al. 1996) and are in line with the results of Foell et al. (Foell et al. 2004) showing that another indicator of neutrophil activation (S100A12) correlates with disease activity in JIA.

We measured also circulating concentrations of TNFα during infliximab treatment. Interestingly, the TNFα levels increased in most of the patients when measured after six months of treatment. Charles et al. found that a single infusion of infliximab elevated the circulating concentrations of immunoreactive but biologically inactive TNFα, and the concentrations declined slowly during the 30 days' follow-up (Charles et al. 1999). In addition, multiple infusions of infliximab have been found to increase TNFα levels in patients with RA (Kopp et al. 2005, Macias et al. 2005) and the data of Kopp et al. support the concept that TNFα is unbound and biologically active (Kopp et al. 2005). In the present study, we were not able to measure whether the immunoreactive TNFα was biologically active or inactive (e.g. due to it had bound to infliximab). It could be hypothesized that when TNFα is neutralized by being bound to chimeric anti-TNFα antibody infliximab, that may result in a lack of negative feedback on the secretion of TNFα, and in fact lead to elevated TNFα production. If treatment with infliximab is then withdrawn for some reason, this increased TNFα production could cause a reactivation of the disease. Interestingly, high serum TNFα levels have also been reported to be associated with a lack of response to

infliximab in Crohn's disease (Martinez-Borra et al. 2002). In RA, patients with high levels of TNFα in the synovial fluid before the infusion of infliximab were found to display the most positive response to anti-TNFα therapy (Ulfgren et al. 2000). On the other hand, Edrees et al. reported that RA patients with low concentrations of serum TNFα before the infliximab infusion responded well to treatment (Edrees et al. 2005). The role of TNFα levels as a determinant to predict the clinical response or the development of tolerance to TNF antagonists remains to be studied.

Soluble TNFα receptors function as endogenous TNFα antagonists. There are two types of TNFα receptors which are cleaved from cell surface receptors by proteolytic enzymes and circulate as soluble forms i.e. sTNFR1 and sTNFR2 (Feldmann et al. 1996, Campbell et al. 2003). The levels of sTNFR1 decreased in the present study, a similar tendency was seen in the levels of sTNFR2. This effect may be linked to the reduced levels of biologically active TNFα encountered following dosing with infliximab. A reduction in soluble TNFα receptor levels during infliximab treatment has also been observed in patients with RA (Charles et al. 1999, Ohshima et al. 1999).

Adhesion molecules E-selectin and ICAM-1 are present on the surface of activated vascular endothelium and mediate leukocyte infiltration into the inflammatory focus, and the expression of these molecules is increased by TNFα (Mojcik and Shevach 1997, Pober 2002). Elevated concentrations of soluble forms of E-selectin and ICAM-1 (i.e. sE-selectin and sICAM-1) have been detected in the active phase of the disease in patients with JIA (De Benedetti et al. 2000, Chen et al. 2002, Bloom et al. 2005), whereas decreased concentrations of soluble sE-selectin and sICAM-1 have been found in patients with RA after anti-TNFα therapy (Tak et al. 1996, Klimiuk et al. 2004). We observed a slight but statistically significant reduction in serum concentrations of soluble E-selectin and sICAM-1 in JIA patients already after six weeks of treatment with infliximab indicative of a rapid effect that may partly explain the reduced leukocyte infiltration and alleviation of joint inflammation seen following infliximab treatment.

The limited number of patients, the aggressive nature of the disease (resistance to DMARD treatment), and the fact that the blood samples for

cytokine measurements were taken just prior to the scheduled infliximab infusion (i.e. at the time point where the drug effect was likely to be at its lowest) may have underestimated the effects of infliximab treatment on some of the measured inflammatory factors.

3 Drug survival with anti-TNFα treatment in patients with rheumatoid arthritis or spondyloarthropathy

All 200 patients included in the present study were treated in the Tampere University Hospital that provides specialist care for a population of 530.000 in Pirkanmaa Health Care District, including the city of Tampere. In this area, the treatment of RA and SpA with biologicals is confined to one rheumatological centre, i.e. the Center for Rheumatic Diseases, Tampere University Hospital. All patients were initiated with infliximab, or etanercept or adalimumab as their first biological drug treatment.

At the six months' follow-up in patients on infliximab, 74 patients (71%) had achieved at least 50% treatment response and were continuing with the treatment. After the 12 and 24 months' follow-up, 55 (53%) and 41 (40%) patients were continuing with therapy, respectively. Maini et al. reported in their clinical study continuation rates of 82-91% with ACR20 criteria after 7.5 months' treatment depending on the dose and infusion intervals (Maini et al. 1999), and Lipsky et al. reported 73-86% drug survival rates after 13.5 months' treatment with the ACR20 response criteria (Lipsky et al. 2000). In observational studies, continuation rates have been reported to be somewhat lower than in randomized clinical trials, e.g. 82% after 6 months of infliximab treatment (Wendling et al. 2005), and after 12 months' treatment it was 66% (Flendrie et al. 2003) and 85% (Voulgari et al. 2005). At the 24 months' follow-up in the study of Buch et al., only 14% continued infliximab treatment at the 24 months' time-point (Buch et al. 2007). Others have reported 67% (Wendling et al. 2005) and 73% (Voulgari et al. 2005) drug survival rates after 24 months' intervention.

In the present study, 74% and 60% of the etanercept and adalimumab-treated patients, respectively, continued the medication after 12 months of treatment

when ACR50 response was set as the criterion of efficacy. In clinical studies with etanercept, after six months' treatment, 40% of the patients had achieved ACR50 response when etanercept was used as monotherapy (Moreland et al. 1999) and thus rate was elevated to 69% when patients were treated with a combination of etanercept and methotrexate for 13 months (Klareskog et al. 2004). In clinical trials, 22% of the patients on adalimumab as monotherapy with a dose of 40 mg every other week for 26 weeks achieved ACR50 response (van de Putte et al. 2004). In another study, ACR50 response rate was 55% in patients treated for six months with a combination of adalimumab and methotrexate (Weinblatt et al. 2003). The continuation rate in observational studies with etanercept has ranged from 69% to 87% and that of adalimumab from 60% to 83% after 12 months' follow-up (Flendrie et al. 2003, Zink et al. 2005, Brocq et al. 2007). The number of patients continuing with the treatment at the end of the follow-up time in different surveys had varied greatly and is influenced by many factors. The study design, i.e. follow-up time, drug treatment in conjunction with anti-TNFα therapy and continuation/discontinuation criteria, as well the spectrum of patients, all these issues have an effect on outcome.

In infliximab-treated SpA patients, the continuation rate was 44% as compared to 37% in RA patients. The result is in line with a previous Spanish study, where SpA patients had a 33% lower probability to discontinue with the biologicals than RA patients (Carmona et al. 2006) and also Heiberg et al. reported better drug survival among patients with AS or PsA than is the case with RA patients (Heiberg et al. 2008).

In the present study, we were able to retrieve patient records during the follow-ups from practically all patients who had started the treatment with infliximab, etanercept or adalimumab. In fact, only one patient moved to another health care district and was lost to follow-up. A significant loss of patients during follow-up is quite a common phenomenon in many trials, especially in observational studies (Feltelius et al. 2005, Brocq et al. 2007, Mancarella et al. 2007). Compliance with the treatment is enhanced when biological treatment is combined with DMARDs, especially with methotrexate (Kristensen et al. 2006) and this may have influenced the very good adherence to the treatment also in the present study.

In the present study, drug survival of all the three anti-TNFα agents was good although the criteria for treatment continuation was rather strict i.e. ACR50 or a better response. In addition, all patients had refractory disease despite treatment with one or more DMARDs which is the standard treatment in Finland. In addition, good and active treatment of the disease (including glucocorticoid injections into the joints) in a single rheumatological centre where patients were carefully followed is a motivating factor for better drug adherence.

4 Reasons for discontinuation of the anti-TNFα treatment in patients with rheumatoid arthritis or spondyloarthropathy

In infliximab-treated patients, the discontinuation rates after six, 12 and 24 months were 29%, 46% and 60%, respectively. The main reasons for discontinuation were adverse events and lack of efficacy. According to the patients' records, 6 out of 23 patients discontinued the treatment due to an inadequate response during the first seven months, i.e. 17 out of 23 patients experienced an adequate response at the beginning but discontinued the treatment later because of waning efficacy. The same phenomenon has been noticed with many drugs after long term administration, either because of increased metabolism causing decreased concentration of the drug or because of adaptive changes within the affected system (Buxton 2006). Several patients receiving infliximab were unable to maintain an already achieved response at the later time points (Buch et al. 2007) and this was most common during the first year. In observational studies, the discontinuation rate due to inefficacy has varied between 9-11% (Flendrie et al. 2003, Voulgari et al. 2005, Figueiredo et al. 2008) and in clinical studies, it is around 10 % (Maini et al. 1999, Lipsky et al. 2000). Some clinical trials have described about the formation of antibodies against infliximab (Maini et al. 1999, St Clair et al. 2004) and anti-infliximab antibodies are more often found in those patients exhibiting a reduced response (Wolbink et al. 2006). In addition, there is also evidence for an association between antibody formation and increased infliximab clearance (Xu et al. 2008). In the present study, antibodies against infliximab were not measured. It is

possible that the waning efficacy was due to decreased concentrations of active infliximab resulting from the formation of infliximab-antibody-complex (Wolbink et al. 2006) or due individually altered metabolism of infliximab in patients (St Clair et al. 2002).

In the etanercept group, seven patients (13%) discontinued the medication due to lack of efficacy during the first 12 months of treatment. Four patients (9%) treated with adalimumab discontinued the medication because of the same reason. In previous studies, 10% (Hyrich et al. 2007) and 15% (Feltelius et al. 2005) of the patients have discontinued etanercept due to inefficacy. Observational studies with adalimumab have reported discontinuation rates of 11% (Flendrie et al. 2003) and 12% (Hyrich et al. 2007) due to inefficacy. The clinical studies with etanercept and adalimumab monotherapy have reported 15% (Moreland et al. 1999) and 18% (van de Putte et al. 2004) discontinuation rates due to inefficacy during six months' follow-up. Thus, in the present study, the discontinuation rate due to inefficacy is comparable to these previously reported studies although it is worth noting that in these reports the continuation criteria have mostly been set as the ACR20 response, and not the ACR50 value as in the present study which is also the clinical practice in Finland.

5 Adverse events caused discontinuation of anti-TNFα treatment in patients with rheumatoid arthritis or spondyloarthropathy

Adverse events, most often infections and hypersensitivity reactions that required treatment discontinuation, appeared in all treatment groups. In the infliximab-treated patients, six and nine infections were responsible for discontinuation during six and 24 months' follow-up, respectively. This data is in agreement with the results of Curtis et al. who reported a 4-fold greater risk of infections during the first 6 months of infliximab treatment (Curtis et al. 2007). In RA, there is a heightened risk for infections (Mutru et al. 1985, Doran et al. 2002b, Doran et al. 2002c) and the use of conventional DMARDs further increases that risk (Capell 2001, Bernatsky et al. 2007), though contradictory findings have been reported (Lacaille et al. 2008). The use of TNFα antagonists

also amplifies the risk for infections (Listing et al. 2005). Severe lung, skin, soft tissue, joint and bone infections are the most commonly reported infections during infliximab, etanercept and adalimumab treatments and serious generalized infections have been reported as being slightly more probable in RA patients treated with biological agents than in those treated with conventional DMARDs (Listing et al. 2005, Dixon et al. 2006, Salliot et al. 2006). In randomized clinical trials, 16-20% rates of severe adverse events have been depicted depending on the dose and infusion frequency of infliximab and the concomitant DMARDs (Maini et al. 1999, Lipsky et al. 2000).

In the etanercept-treated patients, there was only one case of infection requiring discontinuation of the treatment. There are reports about somewhat different effects for the three TNFα antagonists and this may have a possible effect on the infection risk (Scallon et al. 2002, Nestorov 2005, Furst et al. 2006), as was also observed in the present study. The most common adverse events reported among patients treated with adalimumab were infections. In all, six (14%) patients discontinued treatment due to infections. In the present study, a moderate number of infections appeared compared to the values reported in clinical trials with etanercept and adalimumab (Moreland et al. 1999, Weinblatt et al. 2003, Klareskog et al. 2004, van de Putte et al. 2004).

During the follow-up, one case of tuberculosis occurred during infliximab treatment and it was successfully treated with antimicrobial drugs. Previously, an increased risk of reactivation of tuberculosis has been reported with infliximab treatment (Keane et al. 2001, Gomez-Reino et al. 2003) and in Finland there is routine screening for tuberculosis prior to the commencement of infliximab treatment as designated in the national guidelines. However, it must be stated that the incidence of new and relapsed cases of tuberculosis in Finland is very low, namely 6 cases/100,000 people in 2004 (World Health Organization 2007b), whereas the frequency in other parts of Europe is much higher; 50 cases/100,000 people (World Health Organization 2007a).

Hypersensitivity reactions are quite common adverse events associated with infliximab treatment, but are rarely life threatening. In an observational study, 2.7% of patients had to discontinue infliximab treatment due to a hypersensitivity reaction and the reactions occurred most commonly during the

third or fourth infusion (Wasserman et al. 2004), while in a clinical study, hypersensitivity reactions were most common during the first infusion (Maini et al. 1999). In our study, 5% (six months) and 13% (24 months) of the patients on infliximab discontinued infliximab treatment due to an infusion reaction. At the time when infliximab was introduced, knowledge of infusion reactions was limited and it is possible that some of the patients had their treatment discontinued on insufficient grounds. In the present survey, infusion reactions became more common with time while the incidence of infections remained the same or decreased. Part of the infusion reactions may be explained as a consequence of the formation of antibodies. A more common probabable reason for the infections occurring at the beginning of the treatment may be the fact that the patients' immune system is rapidly undergoing adaptation to the altered cytokine balance during the start of treatment with infliximab.

Injection site reactions are quite commonly associated also with etanercept and adalimumab treatments. In clinical studies with etanercept monotherapy, about 50% rates of injection site reactions have been reported (Moreland et al. 1999, Klareskog et al. 2004) whereas values of 23% were reported when etanercept was used in combination therapy (Klareskog et al. 2004). Adalimumab-treated patients had a 10% injection site reaction rate in monotherapy (van de Putte et al. 2004) and 12% injection site reaction rate in combination therapy (Weinblatt et al. 2003). In the study of Hyrich et al., 22 patients (0.33%) were forced to discontinue anti-TNFα therapy treatment due to an injection site reaction (Hyrich et al. 2007). In the present study, three out of the six adverse events which caused discontinuation were injection site reactions in patients with etanercept, and in adalimumab-treated patients, the corresponding figure was three out of 11 adverse events. These reactions occurred mainly during the first six months of treatment, except for one reaction which appeared after eight months of treatment. Thus, our observations are in line with previous studies and indicate that injection site reactions appear in part of the patients usually during the first months of treatment but they are not predictable.

Three cases of neutropenia were reported. Two cases of neutropenia appeared in infliximab-treated patients, one of them was observed after five and the other

after 24 months of treatment. In addition, one etanercept-treated patient developed cytopenia during the 12 months' follow-up period. In a study with 6739 patients, 38 cases of cytopenias were reported (Hyrich et al. 2007) and in an analysis of 308 adverse events which occurred during TNFα antagonist treatment, there were four patients who developed leukopenias (Konttinen et al. 2006). In addition, there are reports on single cases of leukopenias diagnosed during infliximab treatment (Vidal et al. 2003, Favalli et al. 2005, Wendling et al. 2005, Montane et al. 2007). The European Agency for the Evaluation of Medicinal Products (EMEA), the Committee for Proprietary Medicinal Products (CPMP) stated in October 2000 that etanercept may cause leukopenia and that this should be taken into account when treating patients, although leukopenia is reported rarely (EMEA 2000).

Elevated DNA-antibodies, decreased complement levels and a rash were observed in one patient treated with adalimumab (i.e. SLE-type immunological alterations). There have been sporadic reports in the literature on patients with elevated DNA-antibodies without symptoms of SLE (Charles et al. 2000, Weinblatt et al. 2003).

Elevated aminotransferase activities were observed in one patient in the infliximab group. In an analysis of 248 patients expressing adverse events during anti-TNFα therapy, 21 cases of elevated aminotransferases were reported (Konttinen et al. 2006).

During the period covered in the present study (1999-2005), major changes in the treatment of RA and SpA with TNFα antagonists have taken place, and they probably have influenced the results of the study. Infliximab was the first biological agent marketed in Finland in 1999, and the first of this class of drugs to be used therapeutically in RA. Subsequently, etanercept and adalimumab were introduced. The first patients who received infliximab had very severe and refractory disease that might have influenced the continuation rate of infliximab-treated patients as compared to those treated with etanercept or adalimumab. In the 12 months' drug survival, in infliximab- and adalimumab-treated patients, the reason for discontinuation was most often infection whereas with etanercept it was lack of efficacy. Nearly 10% of infliximab-treated patients discontinued treatment due to remission, while that

was not a reason for discontinuation of etanercept or adalimumab treatment. This probably reflects the change in the clinical practice with respect to the use of TNFα antagonists. At the time when infliximab was first used, the treatment was regarded as intermittent, whereas at the time when two other TNFα antagonists entered into clinical use, it had been appreciated that in most cases continuous treatment is needed for good efficacy. Those reasons as well as the general nature of observational studies and the lack of consistent inclusion / exclusion criteria do not allow direct comparisons between the three biological drugs.

6 Anti-TNFα therapy of rheumatoid arthritis and spondyloarthropathies in the future

TNFα antagonists have revolutionized the treatment of RA, SpA and JIA in recent years. However, about 30% of the patients treated with anti-TNFα therapy still fail to achieve even ACR20 response criteria (Maini 1999, Weinblatt 1999, Lipsky 2000). Therefore novel treatment possibilities are needed and recently three promising biologicals have been introduced, i.e. antibody / fusion protein against IL-6 receptor (tocilizumab) or against T- or B-cell activity (abatacept or rituximab). However, even these drugs which act via a different mechanism of action do not relieve all of symptoms in all patients. The current knowledge of pathogenetic mechanisms of RA and SpA has contributed to the development of biological therapies. It does seem that today's research findings are rapidly translated into tomorrow's clinical practice. The nature of the RA and SpA has also been realized as being multifactorial. For instance in the future RA might well be divided into different subclasses as JIA already is, and that may explain the varied responses to drug treatment at present. As the drug treatment has advanced in giant steps during the last years, there are great hopes for the future and the treatment of RA and SpA is likely to offer multiple possibilities to drug development, such as antibodies against other cytokines and inflammatory cells. However, molecules with totally novel mechanisms of action are needed and these will be based on new discoveries in the pathological mechanisms causing

these diseases, and prescribed to patients individually based on biomarkers characteristic for the subtype of their rheumatic disease.

Summary and conclusions

The aim of the present study was to investigate anti-TNFα therapy in the treatment of RA, SpA and JIA. In the first part of the study, the levels of inflammatory factors were measured in patients with JIA during successful treatment with infliximab. In the second part, drug survival was studied in patients with active and refractory RA or SpA.

The major findings and conclusions were:

1. Serum levels of IL-6, MPO and soluble adhesion molecules sE-selectin and sICAM-1 in patients with JIA decreased during infliximab treatment suggesting in addition to previous data that they are important inflammatory mediators in JIA and their response may partly explain the good clinical effect of TNFα antagonists.
2. Infliximab, etanercept and adalimumab treatment together with one or more DMARDs was effective in patients with DMARD refractory RA or SpA; over half of the patients continued treatment after one year follow-up. The use of concomitant DMARDs or oral glucocorticoids could be reduced and the overall drug survival was good and comparable to previous results from observational studies in patients with less severe disease.
3. The main reasons for discontinuation were infections, hypersensitivity reactions and lack of efficacy or loss of already gained efficacy, which was seen especially during 24 months' follow-up in infliximab-treated patients.
4. Some rare adverse events appeared during anti-TNFα therapy, i.e. leukopenia (3 patients), adenocarcinoma of ovary, and features of drug-induced SLE, and elevation of transaminases.

In conclusion, TNFα antagonists were effective and well tolerated resulting in good drug survival, although especially in infliximab-treated RA and SpA patients, a decrease in efficacy was detected along follow-up. Anti-TNFα therapy

also reduced levels of the inflammatory mediators in JIA patients in conjunction with good clinical response. Despite the good drug survival, some of the patients still continued to have active disease while treated with TNFα antagonist in addition to combination therapy with DMARDs. The pathogenesis of RA and SpA need to be clarified more specifically to find out possible new targets to drug development. New drug molecules for the treatment of RA and SpA are needed as well as the more specific biomarkers as a way of tailoring the drug treatment to meet the needs of the individual patient.

Kiitokset (Acknowledgements)

This study was carried out in the Immunopharmacology Research Group, Medical School, University of Tampere, Finland.

Ensimmäisenä haluan kiittää väitöskirjatyöni ohjaajaa professori Eeva Moilasta. Eeva herätti minussa kiinnostuksen jatkaa tutkimusta tehtyäni syventävien opintojen opinnäytteen hänen ohjauksessaan. Eeva, sinulla on erityinen kyky innostaa ohjattavaasi tieteen tekemisessä ja jopa ylittää itsensä. Näiden vuosien aikana Eeva on myös tarjonnut minulle loistavat mahdollisuudet osallistua kotimaisiin ja kansainvälisiin kokouksiin.

Kiitän myös lämpimästi toista ohjaajaani dosentti Markku Korpelaa. Hänellä on erittäin laaja tietämys ja kokemus reumataudeista sekä niiden lääkehoidosta. Markku on ollut myös avainasemassa kliinisen tiedon keräämisessä.

Kiitos osatöissä mukana olleille dosentti Visa Honkaselle, dosentti Pekka Lahdenteelle sekä professori Markku Hakalalle, joka on toiminut myös seurantaryhmäni jäsenenä. On ollut etuoikeus tehdä yhteistyötä kokeneiden asiantuntijoiden kanssa.

Kiitos väitöskirjatyöni esitarkastajille professori Risto Huupposelle ja dosentti Anneli Savolaiselle, jotka edesauttoivat tarkentavilla ja rakentavilla kommenteillaan väitöskirjani jäsentymistä kirjoitusprosessin loppuvaiheessa. I wish to acknowledge Dr Ewen MacDonald for checking and correcting the English language of the thesis.

Immunofarmakologian tutkimusryhmä on toiminut usean vuoden ajan työpaikkanani. Sekä nykyiset että jo muihin tehtäviin siirtyneet työtoverit ja opiskelijat ovat luoneet hyvän hengen ja mukavan ilmapiirin tehdä töitä. Sen vuoksi aamuviiden herätykset, junamatka Tampereelle ja pyöräily vaikka lumisateessa ovat sujuneet hymyssä suin!

Lämmin kiitos Katriina Vuolteenaholle suuresta työpanoksesta ja avuliaisuudesta osatöiden ja tutkimustyöni eri vaiheissa. Kiitos Riina Niemiselle avusta ensimmäisen osatyöni kanssa ja Marja-Leena Lampénille kiitos

onnistuneiden laboratoriomääritysten tekemisestä. Nöyrät kiitokset Heli Määtälle ”kaikkien mahdollisten asioiden” auttamisessa ja hoitamisessa, aina ne vaan ovat loppujen lopuksi järjestyneet. Mari Hämäläiselle lämpimät kiitokset työhuoneen jakamisesta ja kaikesta tuesta työasioissa sekä hauskoista hetkistä. Suuri kiitos työtoveruudesta Salla Hietakankaalle, Meiju Kukkoselle, Raija Pinolalle, Marja Jousimiehelle, Tiina Leppäselle, Riku Korhoselle, Hannu Kankaanrannalle, Lauri Lehtimäelle, Anna Koskiselle, Erja-Leena Paukkerille, Elina Jaakkolalle, Ulla Jaloselle, Outi Sareilalle sekä Pinja Ilmarinen-Salolle.

Haluan kiittää Tampereen yliopistollisen sairaalan Reumakeskuksen henkilökuntaa heidän auttavaisuudesta ja mukavasta yhteistyöstä.

Ystäviä ja sukulaisia haluan kiittää yhteisistä hetkistä, jotka eivät ole mitenkään liittyneet työhön tai väitöskirjaan, vaan tarjonneet hengähdystauon työn lomassa. Miialle erityiskiitos suuresta ystävyydestä, ilon ja surun hetkistä sekä pitkistä puheluista vaikka yöaikaan! Suuri kiitos appivanhemmille Kepalle ja Pavelle, olette olleet korvaamaton apu.

Hellät kiitokset äidilleni ja edesmenneelle isälleni. Teidän suuri rakkaus, ymmärtämys ja tuki ovat luoneet loistavan pohjan elämälle ja työuralle. Isoveljelleni Timolle sekä hänen perheelleen kiitos yhteisistä ja arvokkaista hetkistä.

Rakas aviomieheni Lasse sekä rakkaat lapsemme Iida ja Kaisa, haluan osoittaa suurimmat ja lämpimimmät kiitokset teille, olette elämäni valo!

This work was supported by the Medical Research Fund of Tampere Universty Hospital, Rheumatism Foundation Hospital, Heinola, Clinical Drug Research Graduate School.

Sipoossa 1.11.2009

Tiina Levälampi

References

Adarichev VA, Vermes C, Hanyecz A, Mikecz K, Bremer EG & Glant TT (2005): Gene expression profiling in murine autoimmune arthritis during the initiation and progression of joint inflammation. Arthritis Res Ther 7(2): R196-R207.

Adebajo AO & Hall MA (1998): The use of intravenous pulsed methylprednisolone in the treatment of systemic-onset juvenile chronic arthritis. Br J Rheumatol 37(11): 1240-1242.

Aho K, Kaipiainen-Seppänen O, Heliövaara M, Klaukka T (1998): Epidemiology of rheumatoid arthritis in Finland. Semin Arthritis Rheum. 27(5): 325-334.

Aho K, Koskenvuo M, Tuominen J & Kaprio J (1986): Occurrence of rheumatoid arthritis in a nationwide series of twins. J Rheumatol 13(5): 899-902.

Akkoc N (2008): Are spondyloarthropathies as common as rheumatoid arthritis worldwide? A review. Curr Rheumatol Rep 10(5): 371-378.

Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Breedveld FC, Dijkmans BA & FARR study group (2006): Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. Clin Exp Rheumatol 24(6 Suppl 43): S-77-82.

Alsalameh S, Winter K, Al-Ward R, Wendler J, Kalden JR & Kinne RW (1999): Distribution of TNF-alpha, TNF-R55 and TNF-R75 in the rheumatoid synovial membrane: TNF receptors are localized preferentially in the lining layer; TNF-alpha is distributed mainly in the vicinity of TNF receptors in the deeper layers. Scand J Immunol 49(3): 278-285.

Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH & Luthra HS (1988): The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31(3): 315-324.

Baraliakos X, Brandt J, Listing J, Haibel H, Sorensen H, Rudwaleit M, Sieper J & Braun J (2005a): Outcome of patients with active ankylosing spondylitis after two years of therapy with etanercept: clinical and magnetic resonance imaging data. Arthritis Rheum 53(6): 856-863.

Baraliakos X, Listing J, Rudwaleit M, Brandt J, Sieper J & Braun J (2005b): Radiographic progression in patients with ankylosing spondylitis after 2 years of treatment with the tumour necrosis factor alpha antibody infliximab. Ann Rheum Dis 64(10): 1462-1466.

Barrera P, Boerbooms AM, Janssen EM, Sauerwein RW, Gallati H, Mulder J, de Boo T, Demacker PN, van de Putte LB & van der Meer JW (1993): Circulating soluble tumor necrosis factor receptors, interleukin-2 receptors, tumor necrosis factor alpha, and interleukin-6 levels in rheumatoid arthritis. Longitudinal evaluation during methotrexate and azathioprine therapy. Arthritis Rheum 36(8): 1070-1079.

Barrera P, Joosten LA, den Broeder AA, van de Putte LB, van Riel PL & van den Berg WB (2001): Effects of treatment with a fully human anti-tumour necrosis factor alpha monoclonal antibody on the local and systemic homeostasis of interleukin 1 and TNFalpha in patients with rheumatoid arthritis. Ann Rheum Dis 60 (7): 660-669.

Barrera P, van der Maas A, van Ede AE, Kiemeney BA, Laan RF, van de Putte LB & van Riel PL (2002): Drug survival, efficacy and toxicity of monotherapy with a fully human anti-tumour necrosis factor-alpha antibody compared with methotrexate in long-standing rheumatoid arthritis. Rheumatology (Oxford) 41(4): 430-439.

Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Genovese MC, Wasko MC, Moreland LW, Weaver AL, Markenson J & Finck BK (2000): A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 343(22): 1586-1593.

Bernatsky S, Hudson M, Suissa S (2007): Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford) 46: 1157-1160.

Bertolini DR, Nedwin GE, Bringman TS, Smith DD & Mundy GR (1986): Stimulation of bone resorption and inhibition of bone formation in vitro by human tumour necrosis factors. Nature 319(6053): 516-518.

Beutler B & Cerami A (1989): The biology of cachectin/TNF--a primary mediator of the host response. Annu Rev Immunol 7: 625-655.

Bingham CO,3rd (2002): The pathogenesis of rheumatoid arthritis: pivotal cytokines involved in bone degradation and inflammation. J Rheumatol Suppl 65: 3-9.

Black RA, Rauch CT, Kozlosky CJ, Peschon JJ, Slack JL, Wolfson MF, Castner BJ, Stocking KL, Reddy P, Srinivasan S, Nelson N, Boiani N, Schooley KA, Gerhart M, Davis R, Fitzner JN, Johnson RS, Paxton RJ, March CJ & Cerretti DP (1997): A metalloproteinase disintegrin that releases tumour-necrosis factor-alpha from cells. Nature 385(6618): 729-733.

Bloom BJ, Nelson SM, Eisenberg D & Alario AJ (2005): Soluble intercellular adhesion molecule-1 and E-selectin as markers of disease activity and endothelial activation in juvenile idiopathic arthritis. J Rheumatol 32(2): 366-372.

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 & van der Linden S (1997): Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 350(9074): 309-318.

van den Bosch F, Kruithof E, Baeten D, Herssens A, de Keyser F, Mielants H, Veys EM (2002): Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (infliximab) versus placebo in active spondylarthropathy. 46(3):755-765.

Bowes J & Barton A (2008): Recent advances in the genetics of RA susceptibility. Rheumatology (Oxford) 47(4): 399-402.

Bradley JR (2008): TNF-mediated inflammatory disease. J Pathol 214(2): 149-160.

Brandt J, Haibel H, Cornely D, Golder W, Gonzalez J, Reddig J Thriene W, Sieper J, Braun J (2000): Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. Arthritis Rheum 43(6): 1346-1352.

Brandt J, Listing J, Haibel H, Sorensen H, Schwebig A, Rudwaleit M, Sieper J & Braun J (2005): Long-term efficacy and safety of etanercept after readministration in patients with active ankylosing spondylitis. Rheumatology (Oxford) 44(3): 342-348.

Braun J & Sieper J (2007): Ankylosing spondylitis. Lancet 369(9570): 1379-1390.

Braun J, Brandt J, Listing J, Zink A, Alten R, Golder W, Gromnica-Ihle E, Kellner H, Krause A, Schneider M, Sörensen H, Zeidler H, Thriene W, Sieper J (2002a): Treatment of active

ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 359 (9313): 1187-1193.

Braun J, Golder W, Bollow M, Sieper J & van der Heijde D (2002b): Imaging and scoring in ankylosing spondylitis. Clin Exp Rheumatol 20(6 Suppl 28): S178-184.

Braun J, Brandt J, Listing J, Zink A, Alten R, Burmester G, Golder W, Gromnica-Ihle E, Kellner H, Schneider M, Sörensen H, Zeidler H, Reddig J, Sieper J (2003): Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebo-controlled trial. 48(8):2224-33.

Braun J, Baraliakos X, Brandt J & Sieper J (2005): Therapy of ankylosing spondylitis. Part II: biological therapies in the spondyloarthritides. Scand J Rheumatol 34(3): 178-190.

Braun J, Landewe R, Hermann KG, Han J, Yan S, Williamson P, van der Heijde D; ASSERT Study Group (2006) Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. Arthritis Rheum (5): 1646-1652.

Braun J, Deodhar A, Dijkmans B, Geusens P, Sieper J, Williamson P, Xu W, Visvanathan S, Baker D, Goldstein N, van der Heijde D, Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group (2008): Efficacy and safety of infliximab in patients with ankylosing spondylitis over a two-year period. Arthritis Rheum 59(9): 1270-1278.

Breedveld FC & Dayer JM (2000): Leflunomide: mode of action in the treatment of rheumatoid arthritis. Ann Rheum Dis 59(11): 841-849.

Breedveld FC, Emery P, Keystone E, Patel K, Furst DE, Kalden JR, St Clair EW, Weisman M, Smolen J, Lipsky PE & Maini RN (2004): Infliximab in active early rheumatoid arthritis. Ann Rheum Dis 63(2): 149-155.

Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL & 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(1): 26-37.

Breit W, Frosch M, Meyer U, Heinecke A & Ganser G (2000): A subgroup-specific evaluation of the efficacy of intraarticular triamcinolone hexacetonide in juvenile chronic arthritis. J Rheumatol 27(11): 2696-2702.

Brennan FM & McInnes IB (2008): Evidence that cytokines play a role in rheumatoid arthritis. J Clin Invest 118(11): 3537-3545.

Brennan FM, Chantry D, Jackson AM, Maini RN & Feldmann M (1989a): Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. Lancet 2(8657): 244-247.

Brennan FM, Chantry D, Jackson AM, Maini RN & Feldmann M (1989b): Cytokine production in culture by cells isolated from the synovial membrane. J Autoimmun 2 Suppl: 177-186.

Brennan FM, Gibbons DL, Mitchell T, Cope AP, Maini RN & Feldmann M (1992): Enhanced expression of tumor necrosis factor receptor mRNA and protein in mononuclear cells isolated from rheumatoid arthritis synovial joints. Eur J Immunol 22(7): 1907-1912.

Bresnihan B, Alvaro-Gracia JM, Cobby M, Doherty M, Domljan Z, Emery P, Nuki G, Pavelka K, Rau R, Rozman B, Watt I, Williams B, Aitchison R, McCabe D & Musikic P (1998): Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 41(12): 2196-2204.

Brewer EJ, Jr, Giannini EH & Barkley E (1980): Gold therapy in the management of juvenile rheumatoid arthritis. Arthritis Rheum 23(4): 404-411.

Brewer EJ, Giannini EH, Kuzmina N & Alekseev L (1986): Penicillamine and hydroxychloroquine in the treatment of severe juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind placebo-controlled trial. N Engl J Med 314(20): 1269-1276.

Brockhaus M, Schoenfeld HJ, Schlaeger EJ, Hunziker W, Lesslauer W & Loetscher H (1990): Identification of two types of tumor necrosis factor receptors on human cell lines by monoclonal antibodies. Proc Natl Acad Sci U S A 87(8): 3127-3131.

Brocq O, Roux CH, Albert C, Breuil V, Aknouche N, Ruitord S, Mousnier A & Euller-Ziegler L (2007): TNFalpha antagonist continuation rates in 442 patients with inflammatory joint disease. Joint Bone Spine 74(2):148-154.

den Broeder A, van de Putte L, Rau R, Schattenkirchner M, Van Riel P, Sander O, Binder C, Fenner H, Bankmann Y, Velagapudi R, Kempeni J & Kupper H (2002): A single dose, placebo controlled study of the fully human anti-tumor necrosis factor-alpha antibody adalimumab (D2E7) in patients with rheumatoid arthritis. J Rheumatol 29(11): 2288-2298.

Brown KD, Claudio E & Siebenlist U (2008): The roles of the classical and alternative nuclear factor-kappaB pathways: potential implications for autoimmunity and rheumatoid arthritis. Arthritis Res Ther 10(4): 212.

Browning JL (2006): B cells move to centre stage: novel opportunities for autoimmune disease treatment. Nat Rev Drug Discov 5(7): 564-576.

Buch MH, Bingham SJ, Bryer D & Emery P (2007): Long-term infliximab treatment in rheumatoid arthritis: subsequent outcome of initial responders. Rheumatology (Oxford) 46(7): 1153-1156.

Buch MH, Vital EM & Emery P (2008): Abatacept in the treatment of rheumatoid arthritis. Arthritis Res Ther 10 Suppl 1: S5.

Buchan G, Barrett K, Turner M, Chantry D, Maini RN & Feldmann M (1988): Interleukin-1 and tumour necrosis factor mRNA expression in rheumatoid arthritis: prolonged production of IL-1 alpha. Clin Exp Immunol 73(3): 449-455.

Burger D, Dayer JM, Palmer G & Gabay C (2006): Is IL-1 a good therapeutic target in the treatment of arthritis? Best Pract Res Clin Rheumatol 20(5): 879-896.

Butler DM, Maini RN, Feldmann M & Brennan FM (1995): Modulation of proinflammatory cytokine release in rheumatoid synovial membrane cell cultures. Comparison of monoclonal anti TNF-alpha antibody with the interleukin-1 receptor antagonist. Eur Cytokine Netw 6(4): 225-230

Buttgereit F, Saag KG, Cutolo M, da Silva JA & Bijlsma JW (2005): The molecular basis for the effectiveness, toxicity, and resistance to glucocorticoids: focus on the treatment of rheumatoid arthritis. Scand J Rheumatol 34(1): 14-21.

Buxton ILO (2006): Pharmacokinetics and pharmacodynamics. The dynamics of drug absorption, distribution, action, and elimination In: Goodman & Gilman's The pharmacologiacal basis of therapeutics, pp. 1-39. Eds. Brunton LL; Lazo JS, Parker KL.

Calin A, Dijkmans BA, Emery P, Hakala M, Kalden J, Leirisalo-Repo M, Mola EM, Salvarani C, Sanmarti R, Sany J, Sibilia J, Sieper J, van der Linden S, Veys E, Appel AM & Fatenejad S (2004): Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis 63(12): 1594-1600.

Campbell IK, O'Donnell K, Lawlor KE & Wicks IP (2001): Severe inflammatory arthritis and lymphadenopathy in the absence of TNF. J Clin Invest 107(12): 1519-1527.

Campbell IK, Roberts LJ & Wicks IP (2003): Molecular targets in immune-mediated diseases: the case of tumour necrosis factor and rheumatoid arthritis. Immunol Cell Biol 81(5): 354-366.

Cannon GW & Kremer JM (2004): Leflunomide. Rheum Dis Clin North Am 30(2): 295-309.

Capell HA (2001): Disease modifying antirheumatic drugs: longterm safety issues. J Rheumatol Suppl 62: 10-15.

Carmona L, Gomez-Reino JJ & BIOBADASER Group (2006): Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis. Data from the Spanish registry BIOBADASER. Arthritis Res Ther 8(3): R72.

Caron G, Delneste Y, Aubry JP, Magistrelli G, Herbault N, Blaecke A, Meager A, Bonnefoy JY & Jeannin P (1999): Human NK cells constitutively express membrane TNF-alpha (mTNFalpha) and present mTNFalpha-dependent cytotoxic activity. Eur J Immunol 29(11): 3588-3595.

Carswell EA, Old LJ, Kassel RL, Green S, Fiore N & Williamson B (1975): An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci U S A 72(9): 3666-3670.

Carty SM, Snowden N, Silman AJ (2003): Should infection still be considered as the most likely triggering factor for rheumatoid arthritis. J Rheumatol 30(3): 425-429.

Cassim B, Mody G & Bhoola K (2002): Kallikrein cascade and cytokines in inflamed joints. Pharmacol Ther 94(1-2): 1-34.

Charles P, Elliott MJ, Davis D, Potter A, Kalden JR, Antoni C, Breedveld FC, Smolen JS, Eberl G, deWoody K, Feldmann M & Maini RN (1999): Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-alpha therapy in rheumatoid arthritis. J Immunol 163(3): 1521-1528.

Charles PJ, Smeenk RJ, De Jong J, Feldmann M & Maini RN (2000): Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. Arthritis Rheum 43(11): 2383-2390.

Chen CY, Tsao CH, Ou LS, Yang MH, Kuo ML & Huang JL (2002): Comparison of soluble adhesion molecules in juvenile idiopathic arthritis between the active and remission stages. Ann Rheum Dis 61(2): 167-170.

Chikanza IC, Roux-Lombard P, Dayer JM & Panayi GS (1993): Tumour necrosis factor soluble receptors behave as acute phase reactants following surgery in patients with rheumatoid arthritis, chronic osteomyelitis and osteoarthritis. Clin Exp Immunol 92(1): 19-22.

Choy EH & Panayi GS (2001): Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 344(12): 907-916.

Clark M, Colombel JF, Feagan BC, Fedorak RN, Hanauer SB, Kamm MA, Mayer L, Regueiro C, Rutgeerts P, Sandborn WJ, Sands BE, Schreiber S, Targan S, Travis S, Vermeire S (2007): American gastroenterological association consensus development conference on the

use of biologics in the treatment of inflammatory bowel disease, June 21-23, 2006. Gastroenterology 133(1) 312-339.

Clark P, Tugwell P, Bennett K & Bombardier C (1989): Meta-analysis of injectable gold in rheumatoid arthritis. J Rheumatol 16(4): 442-447.

Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, Kremer J, Bear MB, Rich WJ & 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. 46(3):614-624.

Collins P & Rhodes J (2006): Ulcerative colitis: diagnosis and management. BMJ 333(7563): 340-343.

Cope AP, Aderka D, Doherty M, Engelmann H, Gibbons D, Jones AC, Brennan FM, Maini RN, Wallach D & Feldmann M (1992): Increased levels of soluble tumor necrosis factor receptors in the sera and synovial fluid of patients with rheumatic diseases. Arthritis Rheum 35(10): 1160-1169.

Cronstein BN (2005): Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis. Pharmacol Rev 57(2): 163-172.

Cummings JR, Keshav S, Travis SP (2008): Medical management of Crohn's disease. BMJ 336(7652) 1062-1066.

Curtis JR, Patkar N, Xie A, Martin C, Allison JJ, Saag M, Shatin D & Saag KG (2007): Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 56(4): 1125-1133.

Da Silva JA, Jacobs JW, Kirwan JR, Boers M, Saag KG, Ines LB, de Koning EJ, Buttgereit F, Cutolo M, Capell H, Rau R & Bijlsma JW (2006): Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis 65(3): 285-293.

Dayer JM, Beutler B & Cerami A (1985): Cachectin/tumor necrosis factor stimulates collagenase and prostaglandin E2 production by human synovial cells and dermal fibroblasts. J Exp Med 162(6): 2163-2168.

De Benedetti F, Vivarelli M, Pignatti P, Oliveri M, Massa M, Pistorio A & Martini A (2000): Circulating levels of soluble E-selectin, P-selectin and intercellular adhesion molecule-1 in patients with juvenile idiopathic arthritis. J Rheumatol 27(9): 2246-2250.

Deleuran BW, Chu CQ, Field M, Brennan FM, Mitchell T, Feldmann M & Maini RN (1992): Localization of tumor necrosis factor receptors in the synovial tissue and cartilage-pannus junction in patients with rheumatoid arthritis. Implications for local actions of tumor necrosis factor alpha. Arthritis Rheum 35(10): 1170-1178.

Dembic Z, Loetscher H, Gubler U, Pan YC, Lahm HW, Gentz R, Brockhaus M & Lesslauer W (1990): Two human TNF receptors have similar extracellular, but distinct intracellular, domain sequences. Cytokine 2(4): 231-237.

Dixon WG & Symmons DP (2007): What effects might anti-TNFalpha treatment be expected to have on cardiovascular morbidity and mortality in rheumatoid arthritis? A review of the role of TNFalpha in cardiovascular pathophysiology. Ann Rheum Dis 66(9): 1132-1136.

Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP & British Society for Rheumatology Biologics Register (2006): Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor

necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 54(8): 2368-2376.

Doan T & Massarotti E (2005): Rheumatoid arthritis: an overview of new and emerging therapies. J Clin Pharmacol 45(7): 751-762.

Doran MF, Pond GR, Crowson CS, O'Fallon WM & Gabriel SE (2002a): Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. Arthritis Rheum 46(3): 625-631.

Doran MF, Crowson CS, Pond GR, O'Fallon WM & Gabriel SE (2002b): Frequency of infection in patients with rheumatoid arthritis compared with controls. Arthritis Rheum 46(9): 2287-2293.

Doran MF, Crowson CS, Pond GR, O'Fallon WM & Gabriel SE (2002c): Predictors of infection in rheumatoid arthritis. Arthritis Rheum 46(9): 2294-2300.

Dougados M, Dijkmans B, Khan M, Maksymowych W, van der Linden S & Brandt J (2002): Conventional treatments for ankylosing spondylitis. Ann Rheum Dis 61 Suppl 3: iii40-50.

Edrees AF, Misra SN & Abdou NI (2005): Anti-tumor necrosis factor (TNF) therapy in rheumatoid arthritis: correlation of TNF-alpha serum level with clinical response and benefit from changing dose or frequency of infliximab infusions. Clin Exp Rheumatol 23(4): 469-474.

Edwards JC & Cambridge G (2001): Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes. Rheumatology (Oxford) 40(2): 205-211.

Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, Stevens RM & Shaw T (2004): Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 350(25): 2572-2581.

Elliott MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Katsikis P, Brennan FM, Walker J, Bijl H & Ghrayeb J (1993): Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. Arthritis Rheum 36(12): 1681-1690.

Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, molen JS, Leeb B, Breedvel MC, Macfarlane JD & Bijl H (1994a): Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 344(8930): 1105-1110.

Elliott MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Bijl H & Woody JN (1994b): Repeated therapy with monoclonal antibody to tumour necrosis factor alpha (cA2) in patients with rheumatoid arthritis. Lancet 344(8930): 1125-1127.

EMEA, The European Agency for the Evaluation of Medicinal Products (2000): Revised EMEA public statement on etanercept (enbrel) – serious hematological reactions and demyelination disorders-. http://www.emea.europa.eu/pdfs/human/press/pus/3087100en.pdf 1.11.2009

Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, Racewicz AJ, van Vollenhoven RF, Li NF, Agarwal S, Hessey EW, Shaw TM & DANCER Study Group (2006): The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum 54(5): 1390-1400.

Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, Alecock E, Lee J & Kremer J (2008): IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 67(11): 1516-1523.

Emery P, Genovese MC, van Vollenhoven R, Sharp JT, Patra K & Sasso EH (2009): Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. J Rheumatol 36(7): 1429-1441.

Favalli EG, Varenna M & Sinigaglia L (2005): Drug-induced agranulocytosis during treatment with infliximab in enteropathic spondyloarthropathy. Clin Exp Rheumatol 23(2): 247-250.

Feijóo M, Túnez I, Tasset I, Montilla P, Pérez-Guijo V, Muñoz-Gomariz E, Ruiz A, Schiotis R, Collantes E (2009): Infliximab reduces myeloperoxidase concentration in chronic inflammatory joint diseases. Pharmacology. 83(4): 211-216.

Feldmann M (2009): Translating molecular insight in autoimmunity into effective therapy. Annu Rev Immunol 27: 1-27.

Feldmann M & Maini RN (2001): Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? Annu Rev Immunol 19: 163-196.

Feldmann M, Brennan FM & Maini RN (1996): Role of cytokines in rheumatoid arthritis. Annu Rev Immunol 14: 397-440.

Feldmann M, Brennan FM, Foxwell BM & Maini RN (2001): The role of TNF alpha and IL-1 in rheumatoid arthritis. Curr Dir Autoimmun 3: 188-199.

Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, Katz LM, Lightfoot R,Jr, Paulus H & Strand V (1995): American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 38(6): 727-735.

Feltelius N, Fored CM, Blomqvist P, Bertilsson L, Geborek P, Jacobsson LT, Lindblad S, Lysholm J, Rantapaa-Dahlqvist S, Saxne T, Klareskog L & ARTIS Group (2005): Results from a nationwide postmarketing cohort study of patients in Sweden treated with etanercept. Ann Rheum Dis 64(2): 246-252.

Feuchtenberger M, Kleinert S, Tony HP, Kneitz C (2008): Psoriatic arthritis: therapeutic principles. Clin Dermatol 26(5): 460-463.

Figueiredo IT, Morel J, Sany J & Combe B (2008): Maintenance and tolerability of infliximab in a cohort of 152 patients with rheumatoid arthritis. Clin Exp Rheumatol 26(1): 18-23.

Firestein GS (2003): Evolving concepts of rheumatoid arthritis. Nature 423(6937): 356-361.

Flendrie M, Creemers MC, Welsing PM, den Broeder AA & van Riel PL (2003): Survival during treatment with tumour necrosis factor blocking agents in rheumatoid arthritis. Ann Rheum Dis 62 Suppl 2: ii30-33.

Foell D, Wittkowski H, Hammerschmidt I, Wulffraat N, Schmeling H, Frosch M, Horneff G, Kuis W, Sorg C & Roth J (2004): Monitoring neutrophil activation in juvenile rheumatoid arthritis by S100A12 serum concentrations. Arthritis Rheum 50(4): 1286-1295.

Fontana A, Hengartner H, Weber E, Fehr K, Grob PJ & Cohen G (1982): Interleukin 1 activity in the synovial fluid of patients with rheumatoid arthritis. Rheumatol Int 2(2): 49-53.

Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, Fischkoff SA & Chartash EK (2003): Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 30(12): 2563-2571.

Furst DE, Wallis R, Broder M & Beenhouwer DO (2006): Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. Semin Arthritis Rheum 36(3): 159-167.

Furst DE, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Sieper J, Emery P, Keystone EC, Schiff MH, Mease P, van Riel PL, Fleischmann R, Weisman MH & Weinblatt ME (2007): Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007. Ann Rheum Dis 66 Suppl 3: iii2-22.

Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, Birbara C, Box J, Natarajan K, Nuamah I, Li T, Aranda R, Hagerty DT & Dougados M (2005): Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med 353(11): 1114-1123.

Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, Woodworth T & Gomez-Reino JJ (2008): Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum 58(10): 2968-2980.

Gerloni V, Cimaz R, Gattinara M, Arnoldi C, Pontikaki I & Fantini F (2001): Efficacy and safety profile of cyclosporin A in the treatment of juvenile chronic (idiopathic) arthritis. Results of a 10-year prospective study. Rheumatology (Oxford) 40(8): 907-913.

Gerloni V, Pontikaki I, Gattinara M, Desiati F, Lupi E, Lurati A, Salmaso A & Fantini F (2005): Efficacy of repeated intravenous infusions of an anti-tumor necrosis factor alpha monoclonal antibody, infliximab, in persistently active, refractory juvenile idiopathic arthritis: results of an open-label prospective study. Arthritis Rheum 52(2): 548-553.

van Gestel AM, Haagsma CJ & van Riel PL (1998): Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 41(10): 1845-1850.

van Gestel AM, Anderson JJ, van Riel PL, Boers M, Haagsma CJ, Rich B, Wells G, Lange ML & Felson DT (1999): ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. American College of Rheumatology European League of Associations for Rheumatology. J Rheumatol 26(3): 705-711.

Giannini EH, Brewer EJ,Jr, Kuzmina N, Shaikov A & Wallin B (1990): Auranofin in the treatment of juvenile rheumatoid arthritis. Results of the USA-USSR double-blind, placebo-controlled trial. The USA Pediatric Rheumatology Collaborative Study Group. The USSR Cooperative Children's Study Group. Arthritis Rheum 33(4): 466-476.

Giannini EH, Barron KS, Spencer CH, Person DA, Baum J, Bernstein BH, Kredich DW, Jacobs JC, Zemel LS & Gibbas D (1991): Auranofin therapy for juvenile rheumatoid arthritis: results of the five-year open label extension trial. J Rheumatol 18(8): 1240-1242.

Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, Fink CW, Newman AJ, Cassidy JT & Zemel LS (1992): Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med 326(16): 1043-1049.

Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A (1997): Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum. 40(7): 1202-9.

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 & 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(11): 3381-3390.

Goldring SR (2003): Pathogenesis of bone and cartilage destruction in rheumatoid arthritis. Rheumatology (Oxford) 42 Suppl 2: ii11-16.

Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD & BIOBADASER Group (2003): Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum 48(8): 2122-2127.

Gotzsche PC & Johansen HK (2004): Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD000189. DOI: 10.1002/14651858.CD000189.pub2.

Grohmann U, Orabona C, Fallarino F, Vacca C, Calcinaro F, Falorni A, Candeloro P, Belladonna ML, Bianchi R, Fioretti MC & Puccetti P (2002): CTLA-4-Ig regulates tryptophan catabolism in vivo. Nat Immunol 3(11): 1097-1101.

Gäre BA & Fasth A (1992): Epidemiology of juvenile chronic arthritis in southwestern Sweden: a 5-year prospective population study. Pediatrics 90(6): 950-958.

Haibel H, Rudwaleit M, Brandt HC, Grozdanovic Z, Listing J, Kupper H, Braun J & Sieper J (2006): Adalimumab reduces spinal symptoms in active ankylosing spondylitis: clinical and magnetic resonance imaging results of a fifty-two-week open-label trial. Arthritis Rheum 54(2): 678-681.

Heiberg MS, Koldingsnes W, Mikkelsen K, Rodevand E, Kaufmann C, Mowinckel P & Kvien TK (2008): The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum 59(2): 234-240.

van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, Braun J; Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group (2005): Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 52(2): 582-591.

van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J, Dougados M, Reveille JD, Wong RL, Kupper H, Davis JC,Jr & ATLAS Study Group (2006): Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 54(7): 2136-2146.

van der Heijde D, Burmester GR, Melo-Gomes JR, Codreanu C, Martin Mola E, Pedersen R, Robertson D, Chang DJ, Koenig AS & Freundlich B (2008a): Inhibition of radiographic progression with combination etanercept and methotrexate in patients with moderately active rheumatoid arthritis previously treated with monotherapy. Ann Rheum Dis 68(7): 1113-1118.

van der Heijde D, Landewe R, Baraliakos X, Houben H, van Tubergen A, Williamson P, Xu W, Baker D, Goldstein N, Braun J & Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group (2008b): Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Arthritis Rheum 58(10): 3063-3070.

van der Heijde D, Schiff MH, Sieper J, Kivitz AJ, Wong RL, Kupper H, Dijkmans BA, Mease PJ, Davis JC,Jr & for the ATLAS Study Group (2009): Adalimumab effectiveness for the

treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. Ann Rheum Dis 68(6): 922-929.

Hirano T, Matsuda T, Turner M, Miyasaka N, Buchan G, Tang B, Sato K, Shimizu M, Maini R & Feldmann M (1988): Excessive production of interleukin 6/B cell stimulatory factor-2 in rheumatoid arthritis. Eur J Immunol 18(11): 1797-1801.

Hoes JN, Jacobs JW, Verstappen SM, Bijlsma JW & van der Heijden GJ (2008): Adverse events of low-to-medium-dose oral glucocorticoids in inflammatory diseases: A meta-analysis. Ann Rheum Dis 68(12):1833-1838.

Hohmann HP, Remy R, Brockhaus M & van Loon AP (1989): Two different cell types have different major receptors for human tumor necrosis factor (TNF alpha). J Biol Chem 264(25): 14927-14934.

Houssiau FA, Devogelaer JP, Van Damme J, de Deuxchaisnes CN & Van Snick J (1988): Interleukin-6 in synovial fluid and serum of patients with rheumatoid arthritis and other inflammatory arthritides. Arthritis Rheum 31(6): 784-788.

Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ & British Society for Rheumatology Biologics Register (2007): Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum 56(1): 13-20.

Ilowite N, Porras O, Reiff A, Rudge S, Punaro M, Martin A, Allen R, Harville T, Sun YN, Bevirt T, Aras G & Appleton B (2009): Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. Clin Rheumatol 28(2): 129-137.

Imboden JB (2009): The Immunopathogenesis of Rheumatoid Arthritis. Annu Rev Pathol 4: 417-434.

Immonen K, Finne P, Hakala M, Kautiainen H, Pettersson T, Grönhagen-Riska C (2008): No improvement in survival of patients with amyloidosis associated with inflammatory rheumatic diseases -- data from the Finnish national registry for kidney diseases. J Rheumatol 35(7): 1334-1338.

Inman RD, Davis JC,Jr, Heijde D, Diekman L, Sieper J, Kim SI, Mack M, Han J, Visvanathan S, Xu Z, Hsu B, Beutler A & Braun J (2008): Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 58(11): 3402-3412.

Johnson PW & Glennie MJ (2001): Rituximab: mechanisms and applications. Br J Cancer 85(11): 1619-1623.

Jones EY, Stuart DI & Walker NP (1989): Structure of tumour necrosis factor. Nature 338(6212): 225-228.

Kaipiainen-Seppänen O & Aho K (2000): Incidence of chronic inflammatory joint diseases in Finland in 1995. J Rheumatol 27(1): 94-100.

Kaipiainen-Seppänen O & Savolainen A (2001): Changes in the incidence of juvenile rheumatoid arthritis in Finland. Rheumatology (Oxford) 40(8): 928-932.

Kaiser R (2008): Incidence of lymphoma in patients with rheumatoid arthritis: a systematic review of the literature. Clin Lymphoma Myeloma 8(2): 87-93.

Karjalainen A, Leirisalo-Repo M & Möttönen T (2005): Miloin valitaan biologinen hoito reumasairauteen? SLL 60(17): 1925-1930.

Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, Papp K, Zrubek J, Mudivarthy S, Mack M, Visvanathan S & Beutler A (2009): Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum 60(4): 976-986.

Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, Hsia EC, Han J, Wagner C, Xu Z, Visvanathan S & Rahman MU (2008): Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum 58(4): 964-975.

Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN & Braun MM (2001): Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 345(15): 1098-1104.

Keffer J, Probert L, Cazlaris H, Georgopoulos S, Kaslaris E, Kioussis D & Kollias G (1991): Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis. EMBO J 10(13): 4025-4031.

Kempeni J (1999): Preliminary results of early clinical trials with the fully human anti-TNFalpha monoclonal antibody D2E7. Ann Rheum Dis 58 Suppl 1: I70-72.

Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, Fischkoff SA & 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(5): 1400-1411.

Keystone E, Heijde D, Mason D,Jr, Landewe R, Vollenhoven RV, Combe B, Emery P, Strand V, Mease P, Desai C & Pavelka K (2008): Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 58(11): 3319-3329.

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, Rahman MU & GO-FORWARD Study (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(6): 789-796.

Khan MA (2002): Update on spondyloarthropathies. Ann Intern Med 136(12): 896-907.

Kitahara K & Kawai S (2007): Cyclosporine and tacrolimus for the treatment of rheumatoid arthritis. Curr Opin Rheumatol 19(3): 238-245.

Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Martin Mola E, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M & TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators (2004): Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 363(9410): 675-681.

Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, Ronnelid J, Harris HE, Ulfgren AK, Rantapää-Dahlqvist S, Eklund A, Padyukov L & Alfredsson L (2006a): 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(1): 38-46.

Klareskog L, Padyukov L, Ronnelid J & Alfredsson L (2006b): Genes, environment and immunity in the development of rheumatoid arthritis. Curr Opin Immunol 18(6): 650-655.

Klaukka T & Kaarela K (2003): Methotrexate is the leading DMARD in Finland. Ann Rheum Dis 62(5): 494; author reply 494-495.

Klimiuk PA, Sierakowski S, Latosiewicz R, Cylwik JP, Cylwik B, Skowronski J & Chwiecko J (2003a): Circulating tumour necrosis factor alpha and soluble tumour necrosis factor receptors in patients with different patterns of rheumatoid synovitis. Ann Rheum Dis 62(5): 472-475.

Klimiuk PA, Sierakowski S, Latosiewicz R, Cylwik JP, Cylwik B, Skowronski J & Chwiecko J (2003b): Interleukin-6, soluble interleukin-2 receptor and soluble interleukin-6 receptor in the sera of patients with different histological patterns of rheumatoid synovitis. Clin Exp Rheumatol 21(1): 63-69.

Klimiuk PA, Sierakowski S, Domyslawska I, Fiedorczyk M & Chwiecko J (2004): Reduction of soluble adhesion molecules (sICAM-1, sVCAM-1, and sE-selectin) and vascular endothelial growth factor levels in serum of rheumatoid arthritis patients following multiple intravenous infusions of infliximab. Arch Immunol Ther Exp 52(1): 36-42.

Knight DM, Trinh H, Le J, Siegel S, Shealy D, McDonough M, Scallon B, Moore MA, Vilcek J, Daddona P & Ghrayeb J (1993): Construction and initial characterization of a mouse-human chimeric anti-tnf antibody. Mol Immunol 30(16): 1443-1453.

Kobayashi S, Momora S, Kamatani N (2008): Molecular aspects of rheumatoid arthritis: role of environmental factors. FEBSJ 275(18): 4456-4462.

Konttinen L, Honkanen V, Uotila T, Pöllänen J, Waahtera M, Romu M, Puolakka K, Vasala M, Karjalainen A, Luukkainen R, Nordström DC & for the ROB-FIN study group (2006): Biological treatment in rheumatic diseases: results from a longitudinal surveillance: adverse events. Rheumatol Int 26(10): 916-922.

Kopp S, Alstergren P, Ernestam S, Nordahl S, Morin P & Bratt J (2005): Reduction of temporomandibular joint pain after treatment with a combination of methotrexate and infliximab is associated with changes in synovial fluid and plasma cytokines in rheumatoid arthritis. Cells Tissues Organs 180(1): 22-30.

Korhonen R & Moilanen E (2009a): Abatacept, a novel CD80/86-CD28 T cell co-stimulation modulator, in the treatment of rheumatoid arthritis. Basic Clin Pharmacol Toxicol 104(4): 276-284.

Korhonen R & Moilanen E (2009b): Anti-CD20 antibody rituximab in the treatment of rheumatoid arthritis. Basic Clin Pharmacol Toxicol
DOI: 10.1111/j.1742-7843.2009.00452.x, Epublished ahead of print.

Korpela M (1993): Rheumatoid arthritis and the kidneys. A cross-sectional study on the prevalence, clinical significance and risk of renal and urinary tract disease in patients with rheumatoid arthritis. p. 164. Publications of the Social Insurance Institution ML:122. Helsinki.

Korpela M, Laasonen L, Hannonen P, Kautiainen H, Leirisalo-Repo M, Hakala M, Paimela L, Blåfield H, Puolakka K, Möttönen T & FIN-RACo Trial Group (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(7): 2072-2081.

Kristensen LE, Saxne T, Nilsson JA & Geborek P (2006): Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther 8(6): R174.

Kumar V, Abbas A & Fausto N (2004): Acute and Chronic Inflammation. In: Robbins and Cotran Pathologic Basis of Disease, pp. 47-86 Elsevier Saunders, Philadelphia.

Kvien TK, Hoyeraal HM & Sandstad B (1986): Azathioprine versus placebo in patients with juvenile rheumatoid arthritis: a single center double blind comparative study. J Rheumatol 13(1): 118-123.

Lacaille D, Guh DP, Abrahamowicz M, Anis AH, Esdaile JM (2008): Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. 59(8): 1074-1081.

Lahdenne P, Vähäsalo P & Honkanen V (2003): Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. Ann Rheum Dis 62(3): 245-247.

Lambert RG, Salonen D, Rahman P, Inman RD, Wong RL, Einstein SG, Thomson GT, Beaulieu A, Choquette D & Maksymowych WP (2007): Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 56(12): 4005-4014.

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 (2002): COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 46(2): 347-356.

Lefkowitz DL & Lefkowitz SS (2001): Macrophage-neutrophil interaction: a paradigm for chronic inflammation revisited. Immunol Cell Biol 79(5): 502-506.

van der Linden S, Valkenburg HA & Cats A (1984): Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 27(4): 361-368.

Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, Smolen JS, Weisman M, Emery P, Feldmann M, Harriman GR, Maini RN & Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study,Group (2000): Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 343(22): 1594-1602.

Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, Gromnica-Ihle E, Antoni C, Herzer P, Kekow J, Schneider M & Zink A (2005): Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum 52(11): 3403-3412.

Loetscher H, Pan YC, Lahm HW, Gentz R, Brockhaus M, Tabuchi H & Lesslauer W (1990): Molecular cloning and expression of the human 55 kd tumor necrosis factor receptor. Cell 61(2): 351-359.

Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Whitmore J & Finck BK (2000): Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 342(11): 763-769.

Lovell DJ, Giannini EH, Reiff A, Jones OY, Schneider R, Olson JC, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Lange M, Finck BK, Burge DJ & Pediatric Rheumatology Collaborative Study Group (2003): Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. Arthritis Rheum 48(1): 218-226.

Lovell DJ, Reiff A, Ilowite NT, Wallace CA, ChonY, Lin SL, Baumgartner SW, Giannini EH & Pediatric Rheumatology Collaborative Study Group (2008a): Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum 58(5): 1496-1504.

Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, Nemcova D, Mouy R, Sandborg C, Bohnsack J, Elewaut D, Foeldvari I, Gerloni V, Rovensky J, Minden K, Vehe RK, Weiner LW, Horneff G, Huppertz HI, Olson NY, Medich JR, Carcereri-De-Prati R, McIlraith MJ, Giannini EH, Martini A, Pediatric Rheumatology Collaborative Study Group & Pediatric Rheumatology International Trials Organisation (2008b): Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med 359(8): 810-820.

Luukkainen R, Isomäki H & Kajander A (1977a): Effect of gold treatment on the progression of erosions in RA patients. Scand J Rheumatol 6(2): 123-127.

Luukkainen R, Kajander A & Isomäki H (1977b): Effect of gold on progression of erosions in rheumatoid arthritis. Better results with early treatment. Scand J Rheumatol 6(3): 189-192.

MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K & Silman AJ (2000): Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum 43(1): 30-37.

Macias I, Garcia-Perez S, Ruiz-Tudela M, Medina F, Chozas N & Giron-Gonzalez JA (2005): Modification of pro- and antiinflammatory cytokines and vascular-related molecules by tumor necrosis factor-a blockade in patients with rheumatoid arthritis. J Rheumatol 32(11): 2102-2108.

MacNaul KL, Hutchinson NI, Parsons JN, Bayne EK, Tocci MJ (1990): Analysis of IL-1 and TNF-α gene expression in human rheumatoid synoviocytes and normal monocytes by in situ hybridization. J Immunol 145(12): 4154-4166.

Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, Antoni C, Leeb B, Elliott MJ, Woody JN, Schaible TF & Feldmann M (1998): Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 41(9): 1552-1563.

Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M & 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(9194): 1932-1939.

Maini RN, Breedveld FC, Kalden JR, Smolen JS, Furst D, Weisman MH, St Clair EW, Keenan GF, van der Heijde D, Marsters PA, Lipsky PE & Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group (2004): Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum 50(4): 1051-1065.

Maini RN, Taylor PC, Szechinski J, Pavelka K, Broll J, Balint G, Emery P, Raemen F, Petersen J, Smolen J, Thomson D, Kishimoto T & CHARISMA Study Group (2006): Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum 54(9): 2817-2829.

Maloney DG, Smith B & Rose A (2002): Rituximab: mechanism of action and resistance. Semin Oncol 29(1 Suppl 2): 2-9.

Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, Falappone PC, Ferrante A, Malesci D, Massara A, Nacci F, Secchi ME, Manganelli S, Salaffi F, Bambara ML, Bombardieri S, Cutolo M, Ferri C, Galeazzi M, Gerli R, Giacomelli R, Grassi W, Lapadula G, Cerinic MM, Montecucco C, Trotta F, Triolo G, Valentini G, Valesini G, Ferraccioli GF & GISEA group (2007): Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. J Rheumatol 34(8): 1670-1673.

Mangge H & Schauenstein K (1998): Cytokines in juvenile rheumatoid arthritis (JRA). Cytokine 10(6): 471-480.

Manners PJ & Bower C (2002): Worldwide prevalence of juvenile arthritis why does it vary so much? J Rheumatol 29(7): 1520-1530.

Marotte H, Maslinski W & Miossec P (2005): Circulating tumour necrosis factor-alpha bioactivity in rheumatoid arthritis patients treated with infliximab: link to clinical response. Arthritis Res Ther 7(1): R149-R155.

Martinez-Borra J, Lopez-Larrea C, Gonzalez S, Fuentes D, Dieguez A, Deschamps EM, Perez-Pariente JM, Lopez-Vazquez A, de Francisco R & Rodrigo L (2002): High serum tumor necrosis factor-alpha levels are associated with lack of response to infliximab in fistulizing Crohn's disease. Am J Gastroenterol 97(9): 2350-2356.

Mitchell KL & Pisetsky DS (2007): Early rheumatoid arthritis. Curr Opin Rheumatol 19(3): 278-283.

Moe N & Rygg M (1998): Epidemiology of juvenile chronic arthritis in northern Norway: a ten-year retrospective study. Clin Exp Rheumatol 16(1): 99-101.

Mohler KM, Torrance DS, Smith CA, Goodwin RG, Stremler KE, Fung VP, Madani H & Widmer MB (1993): Soluble tumor necrosis factor (TNF) receptors are effective therapeutic agents in lethal endotoxemia and function simultaneously as both TNF carriers and TNF antagonists. J Immunol 151(3): 1548-1561.

Mojcik CF & Shevach EM (1997): Adhesion molecules: a rheumatologic perspective. Arthritis Rheum 40(6): 991-1004.

Montane E, Salles M, Barriocanal A, Riera E, Costa J & Tena X (2007): Antitumor necrosis factor-induced neutropenia: a case report with double positive rechallenges. Clin Rheumatol 26(9):1527-1529.

Moreland LW, Margolies G, Heck LW,Jr, Saway A, Blosch C, Hanna R & Koopman WJ (1996): Recombinant soluble tumor necrosis factor receptor (p80) fusion protein: toxicity and dose finding trial in refractory rheumatoid arthritis. J Rheumatol 23(11): 1849-1855.

Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, Ettlinger RE, Cohen S, Koopman WJ, Mohler K, Widmer MB & Blosch CM (1997): Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med 337(3): 141-147.

Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, Weaver AL, Keystone EC, Furst DE, Mease PJ, Ruderman EM, Horwitz DA, Arkfeld DG, Garrison L, Burge DJ, Blosch CM, Lange ML, McDonnell ND & Weinblatt ME (1999): Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 130(6): 478-486.

Moreland LW, Russell AS & Paulus HE (2001): Longterm safety and efficacy of etanercept in patients with rheumatoid arthritis. J Rheumatol 28(6): 1238-1244.

Mutru O, Laakso M, Isomäki H & Koota K (1985): Ten year mortality and causes of death in patients with rheumatoid arthritis. Br Med J (Clin Res Ed) 290(6484): 1797-1799.

Myllykangas-Luosujärvi R, Aho K, Kautiainen H & Isomäki H (1995): Shortening of life span and causes of excess mortality in a population-based series of subjects with rheumatoid arthritis. Clin Exp Rheumatol 13(2): 149-153.

Mäkinen H, Kautiainen H, Hannonen P, Möttönen T, Korpela M, Leirisalo-Repo M, Luukkainen R, Puolakka K, Karjalainen A & Sokka T (2007a): Disease activity score 28 as an instrument to measure disease activity in patients with early rheumatoid arthritis. J Rheumatol 34(10): 1987-1991.

Mäkinen H, Kautiainen H, Hannonen P, Möttönen T, Leirisalo-Repo M, Laasonen L, Korpela M, Blåfield H, Hakola M & Sokka T (2007b): Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. J Rheumatol 34(2): 316-321.

Möttönen T, Hannonen P, Leirisalo-Repo M, Nissila 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, Pälvimäki I, Forsberg S, Koota K & Friman C (1999): Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 353(9164): 1568-1573.

Nedwin GE, Naylor SL, Sakaguchi AY, Smith D, Jarrett-Nedwin J, Pennica D, Goeddel DV & Gray PW (1985): Human lymphotoxin and tumor necrosis factor genes: structure, homology and chromosomal localization. Nucleic Acids Res 13(17): 6361-6373.

Nestorov I (2005): Clinical pharmacokinetics of tumor necrosis factor antagonists. J Rheumatol Suppl 74: 13-18.

Nieminen R, Vuolteenaho K, Riutta A, Kankaanranta H, van der Kraan PM, Moilanen T & Moilanen E (2008): Aurothiomalate inhibits COX-2 expression in chondrocytes and in human cartilage possibly through its effects on COX-2 mRNA stability. Eur J Pharmacol 587(1-3): 309-316.

Nishimoto N, Kishimoto T & Yoshizaki K (2000): Anti-interleukin 6 receptor antibody treatment in rheumatic disease. Ann Rheum Dis 59 Suppl 1: i21-27.

Nishimoto N, Yoshizaki K, Maeda K, Kuritani T, Deguchi H, Sato B, Imai N, Suemura M, Kakehi T, Takagi N & Kishimoto T (2003): Toxicity, pharmacokinetics, and dose-finding study of repetitive treatment with the humanized anti-interleukin 6 receptor antibody MRA in rheumatoid arthritis. Phase I/II clinical study. J Rheumatol 30(7): 1426-1435.

Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Hashimoto J, Azuma J & Kishimoto T (2004): Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum 50(6): 1761-1769.

Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Murata N, van der Heijde D & Kishimoto T (2007): Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis 66(9): 1162-1167.

Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T & Azuma J (2008): Long-term safety and efficacy of tocilizumab, an anti-interleukin-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(10):1580-1584.

Ohshima S, Saeki Y, Mima T, Sasai M, Nishioka K, Ishida H, Shimizu M, Suemura M, McCloskey R & Kishimoto T (1999): Long-term follow-up of the changes in circulating cytokines, soluble cytokine receptors, and white blood cell subset counts in patients with rheumatoid arthritis (RA) after monoclonal anti-TNF alpha antibody therapy. J Clin Immunol 19(5): 305-313.

Oliver JE & Silman AJ (2006): Risk factors for the development of rheumatoid arthritis. Scand J Rheumatol 35(3): 169-174.

Ong CK, Lirk P, Tan CH & Seymour RA (2007): An evidence-based update on nonsteroidal anti-inflammatory drugs. Clin Med Res 5(1): 19-34.

Ostensen M, Hoyeraal HM & Kass E (1988): Tolerance of cyclosporine A in children with refractory juvenile rheumatoid arthritis. J Rheumatol 15(10): 1536-1538.

Ou LS, See LC, Wu CJ, Kao CC, Lin YL & Huang JL (2002): Association between serum inflammatory cytokines and disease activity in juvenile idiopathic arthritis. Clin Rheumatol 21(1): 52-56.

Panes J, Gomollon F, Taxonera C, Hinojosa J, Clofent J & Nos P (2007): Crohn's disease: a review of current treatment with a focus on biologics. Drugs 67(17): 2511-2537.

Pascual V, Allantaz F, Arce E, Punaro M & Banchereau J (2005): Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. J Exp Med 201(9): 1479-1486.

Paulus HE, Egger MJ, Ward JR, Williams HJ (1990): Analysis of improvement in individual rheumatoid arthritis patients treated with disease-modifying antirheumatic drugs, based on the findings in patients treated with placebo. The Cooperative Systematic Studies of Rheumatic Diseases Group. Arthritis Rheum 33(4): 477-484.

Pay S, Musabak U, Erdem H, Simsek I, Pekel A, Sengul A & Dinc A (2005): Chimerical anti-TNF-alpha, infliximab, inhibits neutrophil chemotaxis and production of reactive oxygen species by blocking the priming effect of mononuclear cells on neutrophils. Immunopharmacol Immunotoxicol 27(2): 187-198.

Pennica D, Hayflick JS, Bringman TS, Palladino MA & Goeddel DV (1985): Cloning and expression in Escherichia coli of the cDNA for murine tumor necrosis factor. Proc Natl Acad Sci U S A 82(18): 6060-6064.

Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, Maldonado-Cocco J, Suarez-Almazor M, Orozco-Alcala J, Prieur AM (1998): Revision of the proposed classification criteria for juvenile idiopathic arthritis. J Rheumatol 25(10): 1991-1994.

Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P & International League of Associations for Rheumatology (2004): International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 31(2): 390-392.

Pincus T & Callahan LF (1986): Taking mortality in rheumatoid arthritis seriously--predictive markers, socioeconomic status and comorbidity. J Rheumatol 13(5): 841-845.

Plosker GL & Croom KF (2005): Sulfasalazine: a review of its use in the management of rheumatoid arthritis. Drugs 65(13): 1825-1849.

Pober JS (2002): Endothelial activation: intracellular signaling pathways. Arthritis Res 4 (Suppl 3): S109-S116.

Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB & 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(1): 44-48.

Puolakka K, Kautiainen H, Möttönen T, Hannonen P, Korpela M, Hakala M, Järvinen P, Ahonen J, Forsberg S, Leirisalo-Repo M & FIN-RACo Trial Group (2005): 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(1): 36-41.

Puolakka K, Kautiainen H, Pekurinen M, Möttönen T, Hannonen P, Korpela M, Hakala M, Arkela-Kautiainen M, Luukkainen R, Leirisalo-Repo M & FIN-RACo Trial Group (2006): Monetary value of lost productivity over a five 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(7): 899-904.

van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, Settas L, Bijlsma JW, Todesco S, Dougados M, Nash P, Emery P, Walter N, Kaul M, Fischkoff S & Kupper H (2004): Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 63(5): 508-516.

Quartier P, Taupin P, Bourdeaut F, Lemelle I, Pillet P, Bost M, Sibilia J, Kone-Paut I, Gandon-Laloum S, LeBideau M, Bader-Meunier B, Mouy R, Debre M, Landais P & Prieur AM (2003): Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. Arthritis Rheum 48(4): 1093-1101.

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 (2009): 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 60(5): 1222-1231.

Ravelli A, Moretti C, Temporini F, Rossi F, Magni-Manzoni S, Pistorio A & Martini A (2002): Combination therapy with methotrexate and cyclosporine A in juvenile idiopathic arthritis. Clin Exp Rheumatol 20(4): 569-572.

Ravelli A & Martini A (2007): Juvenile idiopathic arthritis. Lancet 369 (9563): 767-778.

Reiff A, Rawlings DJ, Shaham B, Franke E, Richardson L, Szer IS & Bernstein BH (1997): Preliminary evidence for cyclosporin A as an alternative in the treatment of recalcitrant juvenile rheumatoid arthritis and juvenile dermatomyositis. J Rheumatol 24(12): 2436-2443.

Reveille JD, Frank MD, Arnett MD (2005): Spondyloatrhritis: update on pathogenesis and management. Am J Med 118: 592-603.

Rheumatoid arthritis: Current Care Guideline (2009): Working group set up by Finnish Medical Society Duodecim and Finnish Society for Rheumatology, Helsinki, Finland. (Updated 18.09.2009). Available at www.kaypahoito.fi (in Finnish). (1.11.2009)

Roach DR, Bean AG, Demangel C, France MP, Briscoe H & Britton WJ (2002): TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. J Immunol 168(9): 4620-4627.

Rooney M, David J, Symons J, Di Giovine F, Varsani H & Woo P (1995): Inflammatory cytokine responses in juvenile chronic arthritis. Br J Rheumatol 34(5): 454-460.

van Rossum MA, Fiselier TJ, Franssen MJ, Zwinderman AH, ten Cate R, van Suijlekom-Smit LW, van Luijk WH, van Soesbergen RM, Wulffraat NM, Oostveen JC, Kuis W, Dijkstra PF, van Ede CF & Dijkmans BA (1998): Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum 41(5): 808-816.

van Rossum MA, van Soesbergen RM, Boers M, Zwinderman AH, Fiselier TJ, Franssen MJ, ten Cate R, van Suijlekom-Smit LW, Wulffraat NM, van Luijk WH, Oostveen JC, Kuis W, Dijkmans BA & Dutch Juvenile Idiopathic Arthritis Study group (2007): Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis 66(11): 1518-1524.

Roux-Lombard P, Punzi L, Hasler F, Bas S, Todesco S, Gallati H, Guerne PA & Dayer JM (1993): Soluble tumor necrosis factor receptors in human inflammatory synovial fluids. Arthritis Rheum 36(4): 485-489.

Rudwaleit M & Baeten D (2006): Ankylosing spondylitis and bowel disease. Best Pract Res Clin Rheumatol 20(3): 451-471.

Rudwaleit M, Baraliakos X, Listing J, Brandt J, Sieper J & Braun J (2005): Magnetic resonance imaging of the spine and the sacroiliac joints in ankylosing spondylitis and undifferentiated spondyloarthritis during treatment with etanercept. Ann Rheum Dis 64(9): 1305-1310.

Ruperto N, Murray KJ, Gerloni V, Wulffraat N, de Oliveira SK, Falcini F, Dolezalova P, Alessio M, Burgos-Vargas R, Corona F, Vesely R, Foster H, Davidson J, Zulian F, Asplin L, Baildam E, Consuegra JG, Ozdogan H, Saurenmann R, Joos R, Pistorio A, Woo P, Martini A & Pediatric Rheumatology International Trials Organization (2004): A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. Arthritis Rheum 50(7): 2191-2201.

Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, Wouters C, Silverman ED, Balogh Z, Henrickson M, Apaz MT, Baildam E, Fasth A, Gerloni V, Lahdenne P, Prieur AM, Ravelli A, Saurenmann RK, Gamir ML, Wulffraat N, Marodi L, Petty RE, Joos R, Zulian F, McCurdy D, Myones BL, Nagy K, Reuman P, Szer I, Travers S, Beutler A, Keenan G, Clark J, Visvanathan S, Fasanmade A, Raychaudhuri A, Mendelsohn A, Martini A, Giannini EH, Paediatric Rheumatology International Trials Organisation & Pediatric Rheumatology Collaborative Study Group (2007): A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 56(9): 3096-3106.

Saklatvala J (1986): Tumour necrosis factor alpha stimulates resorption and inhibits synthesis of proteoglycan in cartilage. Nature 322(6079): 547-549.

Salliot C, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S & Dougados M (2006): Infections during tumour necrosis factor-{alpha} blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology (Oxford) 46(2): 327-34.

Savolainen HA, Kautiainen H, Isomäki H, Aho K & Verronen P (1997): Azathioprine in patients with juvenile chronic arthritis: a longterm followup study. J Rheumatol 24(12): 2444-2450.

Saxne T, Palladino MA Jr, Heinegard D, Talal N & Wolleheim FA (1988): Detection of tumor necrosis factor alpha but not tumor necrosis factor beta in rheumatoid arthritis synovial fluid and serum. 31(8): 1041-1045.

Scallon B, Cai A, Solowski N, Rosenberg A, Song XY, Shealy D & Wagner C (2002): Binding and functional comparisons of two types of tumor necrosis factor antagonists. J Pharmacol Exp Ther 301(2): 418-426.

Schreiber S, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, Boivin M, Bernstein CN, Staun M, Thomsen OO, Innes A & CDP870 Crohn's Disease Study Group (2005): A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. Gastroenterology 129(3): 807-818.

Schreiber S, Khaliq-Kareemi M, Lawrance IC, Thomsen OO, Hanauer SB, McColm J, Bloomfield R, Sandborn WJ & PRECISE 2 Study Investigators (2007): Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med 357(3): 239-250.

Seldin MF, Amos CI, Ward R & Gregersen PK (1999): The genetics revolution and the assault on rheumatoid arthritis. Arthritis Rheum 42(6): 1071-1079.

Sieper J, Rudwaleit M, Khan MA & Braun J (2006): Concepts and epidemiology of spondyloarthritis. Best Pract Res Clin Rheumatol 20(3): 401-417.

Silman AJ, MacGregor AJ, Thomson W, Holligan S, Carthy D, Farhan A & Ollier WE (1993): Twin concordance rates for rheumatoid arthritis: results from a nationwide study. Br J Rheumatol 32(10): 903-907.

Silman AJ & Pearson JE (2002): Epidemiology and genetics of rheumatoid arthritis. Arthritis Res 4 (Suppl 3): S265-272.

Silverman E, Mouy R, Spiegel L, Jung LK, Saurenmann RK, Lahdenne P, Horneff G, Calvo I, Szer IS, Simpson K, Stewart JA, Strand V & Leflunomide in Juvenile Rheumatoid Arthritis (JRA) Investigator Group (2005a): Leflunomide or methotrexate for juvenile rheumatoid arthritis. N Engl J Med 352(16): 1655-1666.

Silverman E, Spiegel L, Hawkins D, Petty R, Goldsmith D, Schanberg L, Duffy C, Howard P & Strand V (2005b): Long-term open-label preliminary study of the safety and efficacy of leflunomide in patients with polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 52(2): 554-562.

Simmonds RE & Foxwell BM (2008): Signalling, inflammation and arthritis: NF-kappaB and its relevance to arthritis and inflammation. Rheumatology (Oxford) 47(5): 584-590.

Smith CA, Davis T, Anderson D, Solam L, Beckmann MP, Jerzy R, Dower SK, Cosman D & Goodwin RG (1990): A receptor for tumor necrosis factor defines an unusual family of cellular and viral proteins. Science 248(4958): 1019-1023.

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 & 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(6): 797-804.

Smolen JS, Aletaha D, Koeller M, Weisman MH & Emery P (2007): New therapies for treatment of rheumatoid arthritis. Lancet 370(9602): 1861-1874.

Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, Woodworth T, Alten R & OPTION Investigators (2008): Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet 371(9617): 987-997.

Sokka TM, Kautiainen HJ & Hannonen PJ (1997): A retrospective study of treating RA patients with various combinations of slow-acting antirheumatic drugs in a county hospital. Scand J Rheumatol 26(6): 440-443.

Sokka T & Hannonen P (1999): Utility of disease modifying antirheumatic drugs in "sawtooth" strategy. A prospective study of early rheumatoid arthritis patients up to 15 years. Ann Rheum Dis 58(10): 618-622.

St Clair EW, Wagner CL, Fasanmade AA, Wang B, Schaible T, Kavanaugh A, Keystone EC (2002): The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 46(6): 1451-1459.

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 & Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group (2004): Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 50(11): 3432-3443.

Steiner G, Studnicka-Benke A, Witzmann G, Hofler E & Smolen J (1995): Soluble receptors for tumor necrosis factor and interleukin-2 in serum and synovial fluid of patients with rheumatoid arthritis, reactive arthritis and osteoarthritis. J Rheumatol 22(3): 406-412.

Stone M, Salonen D, Lax M, Payne U, Lapp V, Inman R (2001): Clinical and imaging correlates of response to treatment with infliximab in patients with ankylosing spondylitis. J Rheumatol. 28(7): 1605-1614.

Suarez-Almazor ME, Spooner C & Belseck E (2000): Azathioprine for treating rheumatoid arthritis. Cochrane Database Syst Rev (4): CD001461.

Sweeney SE & Firestein GS (2004): Rheumatoid arthritis: regulation of synovial inflammation. Int J Biochem Cell Biol 36(3): 372-378.

Tak PP, Taylor PC, Breedveld FC, Smeets TJ, Daha MR, Kluin PM, Meinders AE & Maini RN (1996): Decrease in cellularity and expression of adhesion molecules by anti-tumor necrosis factor alpha monoclonal antibody treatment in patients with rheumatoid arthritis. Arthritis Rheum 39(7): 1077-1081.

Tan AL, Marzo-Ortega H, O'Connor P, Fraser A, Emery P & McGonagle D (2004): Efficacy of anakinra in active ankylosing spondylitis: a clinical and magnetic resonance imaging study. Ann Rheum Dis 63(9): 1041-1045.

Tannenbaum H, Bombardier C, Davis P, Russell AS & Third Canadian Consensus Conference Group (2006): An evidence-based approach to prescribing nonsteroidal antiinflammatory drugs. Third Canadian Consensus Conference. J Rheumatol 33(1): 140-157.

Thompson RN, Watts C, Edelman J, Esdaile J & Russell AS (1984): A controlled two-centre trial of parenteral methotrexate therapy for refractory rheumatoid arthritis. J Rheumatol 11(6): 760-763.

Torsteinsdottir I, Hakansson L, Hallgren R, Gudbjornsson B, Arvidson NG & Venge P (1999): Serum lysozyme: a potential marker of monocyte/macrophage activity in rheumatoid arthritis. Rheumatology (Oxford) 38(12): 1249-1254.

Tracey D, Klareskog L, Sasso EH, Salfeld JG & Tak PP (2008): Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther 117(2): 244-279.

Tynjälä P, Lindahl P, Honkanen V, Lahdenne P & Kotaniemi K (2007): Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. Ann Rheum Dis 66(4): 548-550.

Tynjälä P, Kotaniemi K, Lindahl P, Latva K, Aalto K, Honkanen V & Lahdenne P (2008): Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. Rheumatology (Oxford) 47(3): 339-344.

Tynjälä P, Vähäsalo P, Honkanen V & Lahdenne P (2009): Drug survival of the first and second course of anti-tumour necrosis factor agents in juvenile idiopathic arthritis. Ann Rheum Dis 68(4): 552-557.

Uhlig T, Kvien TK, Glennas A, Smedstad LM & Forre O (1998): The incidence and severity of rheumatoid arthritis, results from a county register in Oslo, Norway. J Rheumatol 25(6): 1078-1084.

Ulfgren AK, Andersson U, Engstrom M, Klareskog L, Maini RN & Taylor PC (2000): Systemic anti-tumor necrosis factor alpha therapy in rheumatoid arthritis down-regulates synovial tumor necrosis factor alpha synthesis. Arthritis Rheum 43(11): 2391-2396.

Vidal F, Fontova R & Richart C (2003): Severe neutropenia and thrombocytopenia associated with infliximab. Ann Intern Med 139(3): W-W63.

Voulgari PV, Alamanos Y, Nikas SN, Bougias DV, Temekonidis TI & Drosos AA (2005): Infliximab therapy in established rheumatoid arthritis: an observational study. Am J Med 118(5): 515-520.

Vuolteenaho K, Moilanen T, Hamalainen M & Moilanen E (2002): Effects of TNFalpha-antagonists on nitric oxide production in human cartilage. Osteoarthritis Cartilage 10(4): 327-332.

Wallace CA, Ruperto N, Giannini E, Childhood Arthritis and Rheumatology Research Alliance, Pediatric Rheumatology International Trials Organization & Pediatric Rheumatology Collaborative Study Group (2004): Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 31(11): 2290-2294.

Wallis RS, Broder M, Wong J, Lee A & Hoq L (2005): Reactivation of latent granulomatous infections by infliximab. Clin Infect Dis 41 Suppl 3: S194-198.

Wanders A, Heijde D, Landewe R, Behier JM, Calin A, Olivieri I, Zeidler H & Dougados M (2005): Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum 52(6): 1756-1765.

Wang J, Al-Lamki RS, Zhang H, Kirkiles-Smith N, Gaeta ML, Thiru S, Pober JS & Bradley JR (2003): Histamine antagonizes tumor necrosis factor (TNF) signaling by stimulating TNF receptor shedding from the cell surface and Golgi storage pool. J Biol Chem 278(24): 21751-21760.

Ware CF (2005): Network communications: lymphotoxins, LIGHT, and TNF. Annu Rev Immunol 23: 787-819.

Wasserman MJ, Weber DA, Guthrie JA, Bykerk VP, Lee P & Keystone EC (2004): Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. J Rheumatol 31(10): 1912-1917.

Weinblatt ME, Coblyn JS, Fox DA, Fraser PA, Holdsworth DE, Glass DN & Trentham DE (1985): Efficacy of low-dose methotrexate in rheumatoid arthritis. N Engl J Med 312(13): 818-822.

Weinblatt ME, Kaplan H, Germain BF, Block S, Solomon SD, Merriman RC, Wolfe F, Wall B, Anderson L & Gall E (1994): Methotrexate in rheumatoid arthritis. A five-year prospective multicenter study. Arthritis Rheum 37(10): 1492-1498.

Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, Jackson CG, Lange M & 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(4): 253-259.

Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, Teoh LA, Fischkoff SA & Chartash EK (2003): Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 48(1): 35-45.

Weinblatt ME, Keystone EC, Furst DE, Kavanaugh AF, Chartash EK & Segurado OG (2006): Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. Ann Rheum Dis 65(6): 753-759.

Weisman MH, Moreland LW, Furst DE, Weinblatt ME, Keystone EC, Paulus HE, Teoh LS, Velagapudi RB, Noertersheuser PA, Granneman GR, Fischkoff SA & Chartash EK (2003): Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther 25(6): 1700-1721.

Wendling D, Materne GE, Michel F, Lohse A, Lehuede G, Toussirot E, Massol J & Woronoff-Lemsi MC (2005): Infliximab continuation rates in patients with rheumatoid arthritis in everyday practice. Joint Bone Spine 72(4): 309-312.

Westacott CI, Atkins RM, Dieppe PA & Elson CJ (1994): Tumor necrosis factor-alpha receptor expression on chondrocytes isolated from human articular cartilage. J Rheumatol 21(9): 1710-1715.

Williams HJ, Willkens RF, Samuelson CO,Jr, Alarcon GS, Guttadauria M, Yarboro C, Polisson RP, Weiner SR, Luggen ME & Billingsley LM (1985): Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis. A controlled clinical trial. Arthritis Rheum 28(7): 721-730.

Wolbink GJ, Vis M, Lems W, Voskuyl AE, de Groot E, Nurmohamed MT, Stapel S, Tak PP, Aarden L & Dijkmans B (2006): Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis Rheum 54(3): 711-715.

Wolfe F (2000): The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis. J Rheumatol 27(3): 630-637.

Wong JB, Ramey DR & Singh G (2001): Long-term morbidity, mortality, and economics of rheumatoid arthritis. Arthritis Rheum 44(12): 2746-2749.

Wong PK, Campbell IK, Egan PJ, Ernst M & Wicks IP (2003): The role of the interleukin-6 family of cytokines in inflammatory arthritis and bone turnover. Arthritis Rheum 48(5): 1177-1189.

Woo P, Wilkinson N, Prieur AM, Southwood T, Leone V, Livermore P, Wythe H, Thomson D & Kishimoto T (2005): Open label phase II trial of single, ascending doses of MRA in Caucasian children with severe systemic juvenile idiopathic arthritis: proof of principle of the efficacy of IL-6 receptor blockade in this type of arthritis and demonstration of prolonged clinical improvement. Arthritis Res Ther 7(6): R1281-1288.

World Health Organization (2007a): Global and regional incidence of tuberculosis / WHO http://www.who.int/mediacentre/factsheets/fs104/en/index.html#global (1.11.2009).

World Health Organization (2007): Tuberculosis country profile / Finland / WHO. http://apps.who.int/globalatlas/dataQuery/reportData.asp?rptType=1 (1.11.2009).

Xu Z, Seitz K, Fasanmade A, Ford J, Williamson P, Xu W, Davis HM & Zhou H (2008): Population pharmacokinetics of infliximab in patients with ankylosing spondylitis. J Clin Pharmacol 48(6): 681-695.

Yilmaz M, Kendirli SG, Altintas D, Bingol G & Antmen B (2001): Cytokine levels in serum of patients with juvenile rheumatoid arthritis. Clin Rheumatol 20(1): 30-35.

Yokota S, Miyamae T, Imagawa T, Katakura S, Kurosawa R & Mori M (2005): Clinical study of tocilizumab in children with systemic-onset juvenile idiopathic arthritis. Clin Rev Allergy Immunol 28(3): 231-238.

Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, Iwata N, Umebayashi H, Murata T, Miyoshi M, Tomiita M, Nishimoto N & Kishimoto T (2008): Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet 371(9617): 998-1006.

Zhou H, Jang H, Fleischmann RM, Bouman-Thio E, Xu Z, Marini JC, Pendley C, Jiao Q, Shankar G, Marciniak SJ, Cohen SB, Rahman MU, Baker D, Mascelli MA, Davis HM & Everitt DE (2007): Pharmacokinetics and safety of golimumab, a fully human anti-TNF-alpha monoclonal antibody, in subjects with rheumatoid arthritis. J Clin Pharmacol 47(3): 383-396.

Zink A, Listing J, Kary S, Ramlau P, Stoyanova-Scholz M, Babinsky K, von Hinueber U, Gromnica-Ihle E, Wassenberg S, Antoni C, Herzer P, Kekow J, Schneider M & Rau R (2005): Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis 64(9): 1274-1279.

Original communications

The author acknowledges permissions from the following copyright owners to reprint the original communications:

I & II Scandinavian Journal of Rheumatology
Informa Healthcare, London, UK

III & IV International Rheumatology
Springer-Verlag, Berlin, Germany

Effects of infliximab on cytokines, myeloperoxidase, and soluble adhesion molecules in patients with juvenile idiopathic arthritis

T Levälampi[1,2], V Honkanen[3], P Lahdenne[3], R Nieminen[1], M Hakala[2,4], E Moilanen[1]

[1]The Immunopharmacology Research Group, Medical School, University of Tampere and Research Unit, Tampere University Hospital, Tampere, [2]Rheumatism Foundation Hospital, Heinola, [3]Hospital for Children and Adolescents, University of Helsinki, Helsinki University Hospital, Helsinki, and [4]Department of Musculoskeletal Medicine, Medical School, University of Tampere, Tampere, Finland

Objective: Infliximab is effective and well tolerated in the treatment of juvenile idiopathic arthritis (JIA). The aim of the present study was to measure circulating levels of inflammatory mediators in patients with JIA during treatment with infliximab.
Methods: Eight patients with active JIA refractory to standard treatments were treated with infliximab (3–4 mg/kg) at weeks 0, 2 and 6 and thereafter at approximately 6-week intervals up to 24 weeks.
Results: All patients (n=8) responded to the treatment. By 6 weeks of treatment the number of active joints had reduced from 16 ± 4 (mean $\pm$ SEM) to 4 ± 1 ($p < 0.01$) and C-reactive protein (CRP) levels had fallen from 31 ± 8 to 8 ± 3 ($p < 0.001$). Infliximab treatment also reduced the serum concentrations of interleukin-6 (IL-6), myeloperoxidase (MPO), and soluble adhesion molecules ICAM-1 (intercellular adhesion molecule-1), and E-selectin. Tumour necrosis factor-α (TNFα) levels tended to increase while the concentrations of endogenous TNF antagonists (sTNF-RI and sTNF-RII) reduced in most patients during treatment.
Conclusions: Infliximab reduced serum levels of IL-6, MPO and soluble adhesion molecules in JIA patients, producing a good clinical response to the treatment.

The chimeric monoclonal anti-tumour necrosis factor-α (TNFα) antibody infliximab is anti-inflammatory, anti-erosive and well tolerated in the treatment of rheumatoid arthritis (RA) (1, 2) and juvenile idiopathic arthritis (JIA) (3, 4). Inflammation is characterized by an extensive network of cytokines with overlapping effects. Thus it is of interest that inhibition of a single cytokine, TNFα, results in a profound anti-inflammatory and anti-erosive effect in arthritis. This may be explained by the concept that TNFα is at the top of the cytokine cascade and regulates the expression and activity of an array of other inflammatory factors (5). However, the networks regulated by TNFα in vivo are not known in detail. In addition, it is not known which cytokines and inflammatory factors are associated with a favourable clinical response to the treatment with TNFα blockers.

The aim of the present study was to measure circulating levels of cytokines and soluble adhesion molecules in patients with JIA during treatment with infliximab.

Eeva Moilanen, University of Tampere, Medical School/ Pharmacology, FIN-33014, University of Tampere, Finland.
E-mail: eeva.moilanen@uta.fi

Accepted 3 October 2006

Patients and methods

Patients

Eight patients (Table 1) with JIA (3, 6) were included in the study. All patients had an active disease refractory to standard treatments, which included different combinations of methotrexate (MTX), prednisolone, cyclosporin A, sulfasalazine and/or hydroxychloroquine and intra-articular glucocorticoid injections.

Study protocol

Infliximab (3–4 mg/kg) was given at weeks 0, 2 and 6 and thereafter at approximately 6-week intervals. The patients received concomitant MTX and other anti-rheumatic drugs were discontinued. Non-steroidal anti-inflammatory drugs were used as symptomatic treatment. Blood samples were taken at weeks 0, 6, 12 and 24 just before infliximab infusion.

Clinical response was assessed by an experienced paediatric rheumatologist before the first infliximab infusion and at weeks 6, 12 and 24. The study was approved by the ethical committee of Helsinki University Hospital. Patients and parents gave written informed consent before the commencement of the study.

DOI: 10.1080/03009740601089234

Table 1. Patient characteristics.

Patient no.	Sex (F/M)	Age (years)	Diagnosis	Disease duration (years)	HLAB27	Rheumatoid factor	Anti-nuclear antibodies	Iritis
1	F	9	Extended oligoarthritis	3	Negative	Negative	Positive	Yes
2	F	12	Polyarthritis	10	Negative	Negative	Negative	Yes
3	M	13	Extended oligoarthritis	8	Positive	Negative	Positive	Yes
4	F	7	Polyarthritis	5	Negative	Negative	Positive	Yes
5	M	9	Polyarthritis	1	Negative	Negative	Negative	No
6	F	5	Extended oligoarthritis	3	Positive	Negative	Negative	No
7	M	10	Polyarthritis	3	Negative	Negative	Negative	Yes
8	F	12	Polyarthritis	10	Negative	Negative	Negative	Yes

Inflammatory mediators

Serum samples were stored at –70℃ until analysed. Myeloperoxidase (MPO) was measured by radioimmunoassay (Pharmacia & Upjohn, Uppsala, Sweden). Other factors were measured by enzyme immunoassay using the following commercial systems: interleukin (IL)-6 and IL-10 (PeliPair™, Sanquin Reagents, Amsterdam, the Netherlands), IL-1Ra and soluble TNFα receptors I and II (sTNF-RI, sTNF-RII) and TNFα (Quantikine™ Immunoassay, R&D Systems, Minneapolis, MN, USA), IL-18 (MBL ELISA, Medical and Biological Laboratories Co. Ltd, Nagoya, Japan), and soluble intercellular adhesion molecule-1 (sICAM-1) and sE-selectin (HyCult Biotechnology, Uden, the Netherlands).

Statistical analysis

The results are expressed as mean ± standard error of the mean (SEM). Repeated measures analysis of variance followed by the Bonferroni multiple comparisons test was used in the statistical analysis. $p < 0.05$ was considered significant.

Results

All patients (n=8) responded favourably to infliximab treatment (Table 2). During the 6 weeks of treatment the number of active joints reduced from 16 ± 4 (mean ± SEM) to 4 ± 1 ($p < 0.01$) and C-reactive protein (CRP) levels fell from 31 ± 8 to 8 ± 3 ($p < 0.001$). Serum concentrations of IL-6 and MPO reduced during treatment. IL-6 and MPO levels were about 50% and 35% lower, respectively, after 6 weeks than before the treatment and remained low during the 24 weeks of treatment (Figure 1A and B). Soluble TNFα receptors sTNF-RI and sTNF-RII have a role as endogenous TNFα antagonists (7). sTNF-RI concentrations in serum decreased during the treatment (from 1381 to 1118 ng/mL, $p < 0.01$, Table 2).

Table 2. Effects of infliximab treatment on clinical parameters and inflammatory mediators in patients with juvenile idiopathic arthritis (JIA).

	Duration of treatment (weeks)			
Parameter	0	6	12	24
Active joints	16.3 ± 4.4	3.6 ± 1.2**	3.4 ± 1.2**	4.4 ± 2.3**
Swollen joints	13.3 ± 4.8	2.1 ± 1.0*	3.9 ± 1.2	2.4 ± 1.4*
CRP (mg/L)	31 ± 7.8	8.4 ± 3.1**	9.3 ± 3.5**	6.6 ± 1.5***
ESR (mm/h)	38.9 ± 5.5	17.4 ± 2.8***	15.8 ± 2.8***	18.1 ± 4.4***
IL-6 (pg/mL)	14.6 ± 3.4	7.6 ± 2.0*	7.2 ± 1.3*	8.4 ± 2.2
IL-18 (pg/mL)	292 ± 44.3	262 ± 24.3	282 ± 28.8	285 ± 34.0
MPO (ng/mL)	584 ± 121	373 ± 55.7*	368 ± 41.1*	373 ± 66.1*
IL-10 (pg/mL)	2.3 ± 0.6	2.3 ± 0.5	2.1 ± 0.4	2.2 ± 0.4
IL-1Ra (pg/mL)	793 ± 303	459 ± 104	546 ± 88.1	573 ± 84.5
sTNF-RI (pg/mL)	1381 ± 127	1137 ± 69.6*	1242 ± 94.7	1118 ± 94.6**
sTNF-RII (pg/mL)	2251 ± 285	1971 ± 170	2045 ± 234	2092 ± 238
TNF-α (pg/mL)	20.8 ± 6.0	28.7 ± 10.9	28.1 ± 8.4	51.3 ± 11.1
sICAM-1 (ng/mL)	145 ± 5.4	129 ± 8.6***	135 ± 7.7**	134 ± 7.1**
sE-selectin (ng/mL)	68.2 ± 6.5	57.0 ± 6.0**	63.1 ± 7.0	62.6 ± 7.0

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; MPO, myeloperoxidase; sTNF-R, soluble tumour necrosis factor-α receptor; TNFα, tumour necrosis factor-α; sICAM-1, soluble intercellular adhesion molecule 1. Mean ± SEM, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

The mean levels of sTNF-RII decreased to some extent but the difference was not statistically significant (Table 2). TNFα concentration increased in six out of the eight patients, and the mean increase during 6 months of treatment was about 150% (Table 2). Soluble forms of adhesion molecules sE-selectin and sICAM-1 were detectable in serum samples from JIA patients. The levels of sE-selectin and sICAM-1 reduced by 15% and 10%, respectively, during infliximab treatment (Table 2). Infliximab treatment did not alter the serum concentrations of IL-1Ra, IL-10 and IL-18 (Table 2).

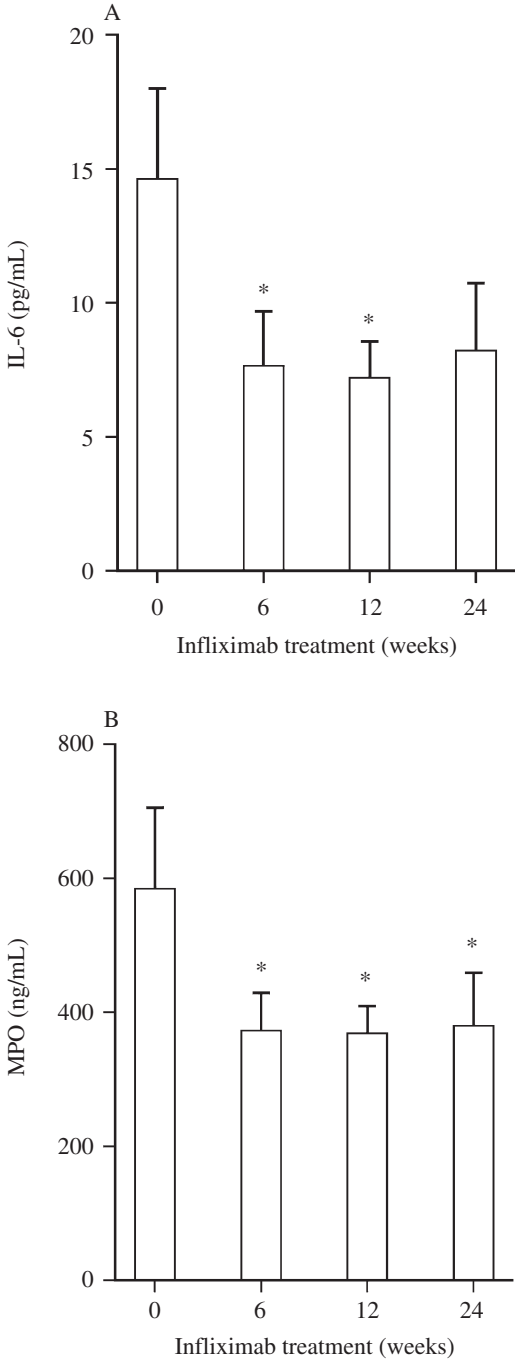

Figure 1. Effects of infliximab treatment on serum (A) interleukin-6 (IL-6) and (B) myeloperoxidase (MPO) levels in patients with juvenile idiopathic arthritis (JIA). Mean ± SEM, n=8. *p<0.05.

Discussion

Infliximab is found to be effective in RA (1, 2) and recently also in JIA (3, 4). In the present study, the clinical response of JIA patients to infliximab treatment was evidenced by the reduced number of swollen and active joints, and CRP and erythrocyte sedimentation rate (ESR) levels. Serum concentrations of IL-6, MPO and soluble adhesion molecules also reduced, along with a good clinical response.

The results should be regarded as preliminary because of the open and uncontrolled design of the study and the limited number of patients. The small number of patients, the aggressive nature of the disease (as evidenced by resistance to standard treatments) and the fact that the blood samples were taken just before the scheduled infliximab infusion (i.e. at the time point where the drug effect was likely to be at its lowest) may underestimate the effects of infliximab on the mediators. However, clear treatment-related effects were seen in many of the inflammatory factors despite the absence of systemic onset JIA patients, who more often have the TNF A2 allele (8) and higher TNFα levels than other JIA patients (9). The results extend the previous data on the molecular effects of infliximab and, to our knowledge, there are no previous reports on the effects of infliximab on cytokine levels in JIA patients. It remains to be studied if any of these mediators would have a predictive value in the treatment of JIA.

IL-6 has a pivotal role in arthritis (10). In the present study, infliximab reduced circulating IL-6 levels by about 50% in 6 weeks, and the effect remained during 24 weeks of treatment. Infliximab has previously been shown to reduce circulating IL-6 levels also in RA (11, 12).

MPO is an enzyme released by activated neutrophils and increased MPO levels have been reported in RA (13). MPO functions as a cytotoxic and immunoregulatory molecule that induces the production of proinflammatory cytokines in macrophages through activating mannose receptors (14). In this study, MPO levels reduced by about 35% in 6 weeks and remained at that lower level during the 24 weeks of treatment. To our knowledge, the effect of infliximab on serum MPO levels has not been reported previously. The results support the significance of neutrophils in JIA (15) and are in line with the results of Foell et al (16) showing that another

indicator of neutrophil activation (S100A12) correlates with disease activity in JIA.

During the 24 weeks of treatment, TNFα levels increased in six of our eight JIA patients. Previously, a single infliximab infusion was found to increase circulating concentrations of immunoreactive but biologically inactive TNFα in RA (11). Multiple infusions of infliximab to RA patients were reported to increase biologically active TNFα levels (17). We were not able to measure whether the TNFα was biologically active or inactive (e.g. due to binding to infliximab). It may be hypothesized that neutralization of TNFα by infliximab could result in a lack of negative feedback on the secretion of TNFα, and lead to increased TNFα production. If infliximab treatment is then withdrawn, the increased TNFα production may cause reactivation of the disease.

Soluble TNFα receptors, cleaved from the cell surface by proteolytic enzymes, function as endogenous TNFα antagonists (7). The levels of sTNF-RI decreased in the present study and a similar tendency was seen in the levels of sTNF-RII. This effect may be linked to altered levels of biologically active TNFα. A reduction in soluble TNFα receptor levels during infliximab treatment has also been seen in patients with RA (11).

Adhesion molecules E-selectin and ICAM-1 are expressed on activated endothelium and mediate leucocyte infiltration into the inflammatory focus. Increased adhesion molecule expression by TNFα at sites of inflammation is reflected in increased levels of their soluble forms (18). Elevated sE-selectin and sICAM-1 concentrations have been measured in active JIA (19–21). Anti-TNFα therapy has been found to decrease sE-selectin and sICAM-1 concentrations in RA patients (15, 22). We found reduced sE-selectin and sICAM-1 levels in JIA patients after 6 weeks of treatment, suggesting a rapid effect that may partly explain the reduced leucocyte infiltration and joint inflammation caused by infliximab.

Blocking of TNFα results in a significant anti-inflammatory and anti-erosive effect in arthritis (5), although chronic arthritis has been associated with altered expression of more than 400 inflammatory genes (23). The present study provides information on the inflammatory mediators regulated by TNFα in vivo and supports the role of TNFα in orchestrating the inflammatory response in JIA.

Acknowledgements

We thank Marja-Leena Lampén for excellent technical assistance and Heli Määttä for skilful secretarial help. This study was supported by The Finnish Graduate School: clinical drug research planning, performance, and critical evaluation, The Rheumatism Foundation Hospital and The Medical Research Fund of Tampere University Hospital, Finland.

References

1. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. 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 1999;354:1932–9.
2. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000;343:1594–602.
3. Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. Ann Rheum Dis 2003;62:245–7.
4. Gerloni V, Pontikaki I, Gattinara M, Desiati F, Lupi E, Lurati A, et al. Efficacy of repeated intravenous infusions of an anti-tumor necrosis factor alpha monoclonal antibody, infliximab, in persistently active, refractory juvenile idiopathic arthritis: results of an open-label prospective study. Arthritis Rheum 2005;52:548–53.
5. Feldmann M, Maini RN. Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? Annu Rev Immunol 2001;19:163–96.
6. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202–9.
7. Campbell IK, Roberts LJ, Wicks IP. Molecular targets in immune-mediated diseases: the case of tumour necrosis factor and rheumatoid arthritis. Immunol Cell Biol 2003;81: 354–66.
8. Modesto C, Patino-Garcia A, Sotillo-Pineiro E, Merino J, Garcia-Consuegra J, Merino R, et al. TNF-alpha promoter gene polymorphisms in Spanish children with persistent oligoarticular and systemic-onset juvenile idiopathic arthritis. Scand J Rheumatol 2005;34:451–4.
9. Mangge H, Kenzian H, Gallistl S, Neuwirth G, Liebmann P, Kaulfersch W, et al. Serum cytokines in juvenile rheumatoid arthritis. Correlation with conventional inflammation parameters and clinical subtypes. Arthritis Rheum 1995;38:211–20.
10. Wong PK, Campbell IK, Egan PJ, Ernst M, Wicks IP. The role of the interleukin-6 family of cytokines in inflammatory arthritis and bone turnover. Arthritis Rheum 2003;48:1177–89.
11. Charles P, Elliott MJ, Davis D, Potter A, Kalden JR, Antoni C, et al. Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-alpha therapy in rheumatoid arthritis. J Immunol 1999;163:1521–8.
12. Marotte H, Maslinski W, Miossec P. Circulating tumour necrosis factor-alpha bioactivity in rheumatoid arthritis patients treated with infliximab: link to clinical response. Arthritis Res Ther 2005;7:R149–55.
13. Torsteinsdottir I, Hakansson L, Hallgren R, Gudbjornsson B, Arvidson NG, Venge P. Serum lysozyme: a potential marker of monocyte/macrophage activity in rheumatoid arthritis. Rheumatology (Oxford) 1999;38:1249–54.
14. Lefkowitz DL, Lefkowitz SS. Macrophage–neutrophil interaction: a paradigm for chronic inflammation revisited. Immunol Cell Biol 2001;79:502–6.
15. Tak PP, Taylor PC, Breedveld FC, Smeets TJ, Daha MR, Kluin PM, et al. Decrease in cellularity and expression of adhesion molecules by anti-tumor necrosis factor alpha monoclonal antibody treatment in patients with rheumatoid arthritis. Arthritis Rheum 1996;39:1077–81.
16. Foell D, Wittkowski H, Hammerschmidt I, Wulffraat N, Schmeling H, Frosch M, et al. Monitoring neutrophil activation in juvenile rheumatoid arthritis by S100A12 serumconcentrations. Arthritis Rheum 2004;50:1286–95.

17. Kopp S, Alstergren P, Ernestam S, Nordahl S, Morin P, Bratt J. Reduction of temporomandibular joint pain after treatment with a combination of methotrexate and infliximab is associated with changes in synovial fluid and plasma cytokines in rheumatoid arthritis. Cells Tissues Organs 2005;180:22–30.
18. Mojcik CF, Shevach EM. Adhesion molecules: a rheumatologic perspective. Arthritis Rheum 1997;40:991–1004.
19. De Benedetti F, Vivarelli M, Pignatti P, Oliveri M, Massa M, Pistorio A, et al. Circulating levels of soluble E-selectin, P-selectin and intercellular adhesion molecule-1 in patients with juvenile idiopathic arthritis. J Rheumatol 2000;27:2246–50.
20. Chen CY, Tsao CH, Ou LS, Yang MH, Kuo ML, Huang JL. Comparison of soluble adhesion molecules in juvenile idiopathic arthritis between the active and remission stages. Ann Rheum Dis 2002;61:167–70.
21. Bloom BJ, Nelson SM, Eisenberg D, Alario AJ. Soluble intercellular adhesion molecule-1 and E-selectin as markers of disease activity and endothelial activation in juvenile idiopathic arthritis. J Rheumatol 2005;32:366–72.
22. Klimiuk PA, Sierakowski S, Domyslawska I, Fiedorczyk M, Chwiecko J. Reduction of soluble adhesion molecules (sICAM-1, sVCAM-1, and sE-selectin) and vascular endothelial growth factor levels in serum of rheumatoid arthritis patients following multiple intravenous infusions of infliximab. Arch Immunol Ther Exp 2004; 52:36–42.
23. Adarichev VA, Vermes C, Hanyecz A, Mikecz K, Bremer EG, Glant TT. Gene expression profiling in murine autoimmune arthritis during the initiation and progression of joint inflammation. Arthritis Res Ther 2005;7: R196–207.

Infliximab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: adverse events and other reasons for discontinuation of treatment

T Levälampi[1], M Korpela[2], K Vuolteenaho[1], E Moilanen[1]

[1]The Immunopharmacology Research Group, Medical School, University of Tampere and Research Unit, Tampere University Hospital, and [2]Centre for Rheumatic Diseases, Tampere University Hospital, Tampere, Finland

Objective: To determine from single-centre data the treatment continuation, discontinuation, and reasons for discontinuation among the patients with active rheumatoid arthritis (RA) or spondyloarthropathies (SpA) who were treated with infliximab as their first biological anti-rheumatic drug.
Methods: All (n=104) RA and SpA patients who were treated with infliximab as their first biological treatment according to the national guidelines in the Centre for Rheumatic Diseases, Tampere University Hospital during 1999–2005 were analysed at baseline and after 6 months of treatment. The treatment was regarded as ineffective if the response was lower than American College of Rheumatology (ACR) response criteria ACR50 in RA or the reduction of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was lower than 50% or 2 cm in SpA.
Results: After 6 months, 71% of the patients continued infliximab treatment and the prednisolone dose was diminished by 40%. Infliximab was discontinued in 30 patients and seven of them discontinued due to remission. Eight patients were regarded as poor responders. Thirteen patients discontinued because of adverse events, mainly infections and hypersensitivity reactions. One patient discontinued the treatment because of drug-related leucopaenia and one because of elevated aminotransferases.
Conclusion: In this study, infliximab treatment was started in patients who had active disease despite ongoing treatment with combinations of disease-modifying anti-rheumatic drugs (DMARDs). Seventy-eight per cent achieved at least 50% response when infliximab was added to their DMARD treatment. Adverse events, mainly infections and hypersensitivity reactions, were in line with previous reports. Two rare adverse events were reported, one patient with leucopaenia and one with elevated aminotransferases.

Tumour necrosis factor-alpha (TNF-α) is an important proinflammatory cytokine involved in local and systemic inflammation and joint destruction in arthritis (1). Neutralization of TNFα by binding it with the chimeric monoclonal TNFα antibody infliximab results in an anti-inflammatory and anti-erosive effect in rheumatoid arthritis (RA) (2, 3). Infliximab has also been found to be effective and well tolerated in spondyloarthropathies (SpA) (4, 5). Infliximab is generally well tolerated but discontinuations of the treatment due to adverse events (2–4, 6–8), most commonly infections (9–11) and hypersensitivity reactions (12), have been reported.

Our aim was to reveal whether there is a difference in outcomes of infliximab treatment between daily clinical practice and clinical studies. Previous reports using American College of Rheumatology (ACR) response criteria usually prefer ACR20 as the criteria for continuation of the infliximab treatment (2, 3, 8), while in Finland the purpose of the treatment is to achieve clinical remission and the criteria for continuation is ACR50 or better response (13). According to the national guidelines (13), treatment with TNFα antagonists is started if the patient is suffering from continuously active disease despite treatment with combinations of traditional disease-modifying anti-rheumatic drugs (DMARDs). In addition, TNFα antagonist is usually added to the treatment with one or more DMARDs (see 'Patients and methods'). In the present study we analysed all patients with RA or SpA who received infliximab as their first biological treatment on clinical grounds according to the national guidelines. We were also interested in the safety and the outcome of infliximab treatment combined with various DMARDs, and not only with methotrexate (which is the usual case in clinical studies). We determined the number of

Eeva Moilanen, Medical School, University of Tampere, Tampere, FIN-33014, Finland.
E-mail: eeva.moilanen@uta.fi

Accepted 15 August 2007

DOI: 10.1080/03009740701633337

patients who achieved at least 50% response and continued the treatment with infliximab, the number of patients who discontinued the treatment, and the reasons for the discontinuation, and we evaluated adverse events leading to discontinuation of the treatment in more detail.

Patients and methods

All patients in this study were treated in the Department of Internal Medicine, Centre for Rheumatic Diseases, Tampere University Hospital, Finland, with commencement of infliximab as their first biological treatment for active RA or SpA during 1999–2005. Indications for biologicals were based on the national recommendations (13). The criteria to start infliximab treatment for RA was that the patient was suffering from continuously active RA [at least six swollen and tender joints, and additionally the duration of morning stiffness should be at least 45 min and/or erythrocyte sedimentation rate (ESR) $\geqslant$30 mmHg and/or serum C-reactive protein (CRP) $\geqslant$28 mg/L] despite treatment with a combination of traditional DMARDs including methotrexate and glucocorticoids (13). The criteria to start biologicals for the treatment of ankylosing spondylitis (AS) were: (i) inefficiency of at least two non-steroidal anti-inflammatory drugs (NSAIDs) for at least 3 months, (ii) sulfasalazine (methotrexate if sulfasalazine was contraindicated) or possibly other DMARDs had been ineffective, and (iii) the patient had an active disease based on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ($\geqslant$4 cm) and on clinical grounds [acute sacroiliitis, elevated acute phase reactants, magnetic resonance imaging (MRI) findings]. In the other spondyloarthropathies such as psoriatic arthritis (PsA) or inflammatory bowel disease (IBD)-associated arthritis, there were no defined criteria to start treatment with biologicals but the decision was made on clinical grounds by an experienced rheumatologist, based on the severity of oligo/polyarthritis and inflammatory axial disease, and the criteria available for RA and AS.

Infliximab infusions at a dose of 3 mg/kg were given in weeks 0, 2, and 6 and every 8 weeks thereafter. Based on the response, the dose was increased or decreased, or the infusion intervals shortened or lengthened. Infliximab was combined usually with methotrexate and sometimes with other DMARDs (mostly sulfasalazine or hydroxychloroquine) and low-dose prednisolone. The clinical response was carefully registered by an experienced rheumatologist at each visit. In RA, the evaluation included ACR response criteria (14), including the number of swollen and tender joints, the physician's assessment of disease activity [Visual Analogue Scale (VAS), 0–10 cm], patient's assessment of general health (VAS), pain (VAS) and the Health Assessment Questionnaire (HAQ), and markers of acute-phase activity (ESR and CRP). A treatment response lower than ACR50 was regarded as ineffective. In AS or SpA, the clinical response included the BASDAI and the Bath Ankylosing Spondylitis Functional Index (BASFI), and the treatment was regarded as ineffective if the reduction in BASDAI was lower than 50% or less than 2 cm.

Concomitant drug treatment that included glucocorticoids, DMARDs, and NSAIDs was documented. The reasons for withdrawal (adverse events, inefficiency, remission, or other reasons) were registered, and severe adverse events were reported to the National Agency for Medicines (NAM), Finland.

Results

Patients

In the present study, all (n=104) RA and SpA patients who received infliximab as their first biological treatment in the Centre for Rheumatic Diseases, Tampere University Hospital, during 1999–2005 were analysed. According to the national guidelines, the criteria to start treatment with a TNFα antagonist is that the patient is suffering from a severe and refractory disease despite active drug treatment. The TNFα antagonist is usually added on to the combination of one or more DMARDs. In this study, 62% of the patients (64 patients) were female, the mean age was 45 years (range 18–75 years), and the mean duration of the disease was 12 years (range 0.8–52 years). Most of the patients (95%) were treated with one or more concomitant DMARDs and 91% were on glucocorticoids in accordance with the national recommendations for infliximab treatment. The patient characteristics are presented in Table 1. Sixty-three (61%) patients had RA and nearly 60% (37 patients) of them had seropositive RA, one-quarter (16 patients) had seronegative RA and about 15% (10 patients) had juvenile idiopathic arthritis (JIA) (Table 2). Forty-one (39%) of the patients had SpA and about 40% (17 patients) of them had AS and nearly 20% (eight patients) PsA. Seronegative oligoarthritis, enteropathic arthritis, reactive arthritis, and sacroiliitis were represented in minor part (Table 2).

Continuation and discontinuation of infliximab treatment, and adverse events compelling the discontinuation of the treatment

The patients' status was assessed 6 months after the initiation of the infliximab treatment. Seventy-four patients (71%) achieved at least 50% treatment response and continued the treatment (Table 1). Thirty patients (29%) discontinued the medication during the 6 months of follow-up (Table 1). There

Table 1. Characteristics of the patients treated with infliximab at the beginning and after 6 months of treatment.

	At the beginning	After 6 months of infliximab treatment					
		Continued	Discontinued				
	All (n=104)	All (n=74)	All (n=30)	Remission (n=7)	Inadequate response (n=8)	Adverse event (n=13)	Other reason (n=2)
Age, years (range)	45 (18–75)	45 (18–76)	47 (22–75)	36 (22–59)	47 (28–56)	53 (28–75)	47 (24–71)
Female (%)	62	57	73	86	50	77	100
Disease duration, years (range)	12 (0.8–52)	13 (1–30)	12 (1–53)	10 (1–26)	6 (2–13)	17 (2–53)	16 (4–29)
Number of concomitant DMARDs							
0 (%)	5	3	20	0	13	23	50
1 (%)	37	41	33	100	25	23	0
2 (%)	29	28	30	0	25	39	50
3 or more (%)	29	28	17	0	37	15	0
Glucocorticoid intake (%)	91	82	83	86	100	77	100
Glucocorticoid dosage (mg/day)	10	5.7	8.7	4.6	16.3	6.1	16.9

DMARD, disease-modifying anti-rheumatic drug.

was no difference in the mean age or disease duration between the patients who continued or discontinued the medication. Forty-three RA patients (68%) continued the treatment and the rate of continuation in patients with SpA was 76% (Table 2). RA patients in all subgroups responded similarly to the treatment (Table 2).

Among the continuers, the number of patients with glucocorticoid treatment decreased from 91% to 82% and the mean equivalent dose of prednisolone decreased from 10.0 ± 0.8 to 5.7 ± 0.5 mg/day (mean $\pm$ SEM, $p < 0.0001$) in 6 months of infliximab treatment. The number of concomitant DMARDs was not changed among the patients who continued the infliximab treatment.

Table 2. Infliximab-treated patients according to the diagnosis.

	At the beginning (n=104)	Continuing after 6 months (n=74; 71%)	
Diagnosis	n	n	%
Rheumatoid arthritis (RA)	63	43	68
Seropositive RA	37	25	68
Seronegative RA	15	11	73
Juvenile idiopathic arthritis (JIA)	10	7	70
Spondyloarthropathy (SpA)	41	31	76
Ankylosing spondylitis	18	11	61
Psoriatic arthritis	8	7	88
Seronegative oligoarthritis	5	5	100
Enteropathic arthritis*	4	3	75
Reactive arthritis	4	3	75
Sacroiliitis	3	2	67

*Crohn's disease, ulcerative colitis.

Table 3. Reasons for discontinuing medication.

Reason	n	%
Remission	7	23
Lack of efficacy	8	27
Adverse event	13	43
Other reason	2	7

The reasons for discontinuation of infliximab treatment are shown in Table 3. Seven patients (23%) achieved remission after the second to fifth infliximab infusion and infliximab treatment was withdrawn. In the frame of the present survey, these seven patients were carefully followed for another 6 months. In that time, two of the patients were compelled to restart infliximab treatment, one after 2 months and one after 6 months because of activation of the disease. Five patients did not restart infliximab treatment during the 6 months' follow-up. Two of these patients had minor activation of the disease immediately after discontinuation of the infliximab treatment, but this diminished rapidly after intensifying the traditional DMARD treatment. Two patients developed minor disease activity, one after 3 months and one after 5 months of remission, but there were no indications to restart infliximab treatment. One patient had no activity in disease during the 6 months' follow-up.

In eight patients (27%) infliximab treatment was regarded as ineffective after the second to sixth infliximab infusion and the treatment was stopped. Thirteen patients (43%) discontinued the medication due to adverse events (Table 4). One 24-year-old female discontinued due to pregnancy and one 71-year-old female patient died due to cerebral infarction during the follow-up. Six (46%) of the adverse events that compelled discontinuation of the treatment were infections and five (38%) were hypersensitivity reactions, which appeared during the fourth or fifth infusion. One patient discontinued the treatment because leucopaenia was found and one because of elevated serum aminotransferases.

Table 4. Adverse events leading to discontinuation of infliximab treatment during the first 6 months.

Classification	No.	Diagnosis	Age (years)	Sex	Disease duration (years)	DMARDs	Time of adverse event	Adverse event
Infection	1	Seropositive rheumatoid arthritis	49	F	6	MTX 10 mg/week CyA 200 mg/day SSZ 2000 mg/day	After third infusion	Pulmonary tuberculosis with mediastinum lymph nodes, diagnosed by biopsy
	2	Seronegative rheumatoid arthritis	51	F	7	PRED 10 mg/day MTX 25 mg/week	After fourth infusion	Infection (CRP 145 mg/mL), with unknown focus
	3	Ankylosing spondylitis	53	M	6	PRED 10 mg/day MTX 25 mg/week CyA 200 mg/day	After fourth infusion	Gluteal abscess
	4	Seropositive rheumatoid arthritis	58	F	26	PRED 15 mg/day ATM 50 mg/6 weeks HCQ 300 mg/day	After second infusion	Septic arthritis of right ankle joint
	5	Ankylosing spondylitis	50	M	12	SSZ 2000 mg/day	After fourth infusion	Pneumopericarditis
	6	Seropositive rheumatoid arthritis	71	F	12	PRED 10 mg/day AF 9 mg/day	After second infusion	Pneumonia
Hypersensitivity reaction	1	Seronegative rheumatoid arthritis	28	F	15		During fourth infusion	Infusion reaction (rash), DMARDs stopped previously because of mild pharyngitis
	2	Juvenile idiopathic arthritis	31	F	30	PRED5 mg/day CyA 100 mg/day SSZ 2000 mg/day AF 3 mg/day	During fourth infusion	Infusion reaction (dyspnoea, rash, and itching)
	3	Seronegative rheumatoid arthritis	40	M	2	PRED 5 mg/day MTX 10 mg/week SSZ 2000 mg/day	During fourth infusion	Infusion reaction (rash)
	4	Psoriatic arthropathy	73	F	15	PRED 10 mg/day	After fourth infusion	Delayed infusion reaction (rash, dyspnoea) developed 2 days after infusion
	5	Seropositive rheumatoid arthritis	75	F	53	PRED 5 mg/day CyA 100 mg/day SSZ 2000 mg/day	During fifth infusion	Infusion reaction (hoarseness, dyspnoea, rash)
Other adverse event	1	Seronegative rheumatoid arthritis	36	F	19	PRED 5 mg/day CyA 100 mg/day SSZ 2000 mg/day	After fourth infusion	Elevation of ALT 125–142 IU/L
	2	Enteropathic arthropathy	58	F	22	PRED 5 mg/day SSZ 1000 mg/day	After fourth infusion	Cytopaenia/neutropaenia (1.4×10^9/L)

DMARD, disease-modifying anti-rheumatic drug; AF, auranofin; ATM, aurothiomalate; CyA, cyclosporin A; HCQ, hydroxychloroquine; MTX, methotrexate; PRED, prednisolone; SSZ, sulfasalazine; ALT, alanine aminotransferase; CRP, C-reactive protein.

Infections

We determined all 13 adverse events that led to discontinuation of infliximab treatment (Table 4). Three of the six infections were pneumonias with bacterial aetiology. Two patients with pneumonia had typical clinical signs and symptoms: fever, dyspnoea, elevated CRP, and radiological findings. The third patient suffered for several months from fluctuating fever and dyspnoea, and she was diagnosed as having tuberculosis.

Before infliximab treatment was started, all patients were screened for tuberculosis according to the national guidelines, which include the patient's history of possible exposure to tuberculosis, thorax X-ray for possible tuberculosis-like changes, and the Mantoux test. The patient who developed tuberculosis during infliximab treatment did not have any known exposure to tuberculosis in her medical history, and at the beginning of infliximab treatment there were no signs of tuberculosis in the chest X-ray and the Mantoux test was negative. After the symptoms had appeared, no signs of tuberculosis were found in the chest X-ray but the Mantoux test turned positive. The symptoms were temporarily relieved by anti-microbial drug treatment but later on an enlargement of the mediastinum was found on a computer tomography (CT) scan. The diagnosis of tuberculosis was confirmed histologically from

lymph nodes obtained by mediastinoscopy 6 months after the first symptoms of pneumonia.

The other infections were as follows: septic arthritis of the ankle joint caused by *Staphylococcus aureus*, gluteal abscess (size: $3.5 \times 1.5 \times 3.7$ cm) with no general symptoms, and generalized infection with elevated CRP (145 mg/L) and no clinically evident infection focus (Table 4). The aetiologies of the last two infections remain unknown.

Hypersensitivity reactions

Five of the 13 adverse events that compelled discontinuation of the infliximab treatment were hypersensitivity reactions (Table 4), with rash and/or dyspnoea as the main symptoms. Four out of the five hypersensitivity reactions occurred during or immediately after the infusion. In one patient, erythema, facial urticaria, and nausea appeared 30 min after the initiation of the fourth infusion. Another patient reported hoarseness during the infusion and developed dyspnoea and rash in the lower limbs after the infusion. One patient developed an extensive rash and flush in the upper body during the fourth infusion. A 31-year-old woman suffered from itching in the mouth, throat, and upper body, and she had also mild dyspnoea. A delayed hypersensitivity reaction (rash, oedema, itching of face, and dyspnoea) occurred 2 days after the fourth infusion in a 73-year-old woman with PsA. All hypersensitivity reactions were relieved after discontinuation of the infliximab infusion and strengthening the glucocorticoid treatment. All but one patient had ongoing glucocorticoid treatment at the time of the hypersensitivity reaction.

Other adverse events

Elevation of aminotransferases (125–142 IU/L) was reported in one patient during the 6-month follow-up. Levels were normalized after discontinuation of infliximab infusions. Another patient developed leucopaenia (neutrophils 1.4×10^9). Conventional DMARDs, sulfasalazine, and methotrexate were discontinued without improvement. Discontinuation of infliximab infusions had a favourable response and leucocyte levels were normalized.

Discussion

Tampere University Hospital serves as a specialist care centre for a population of 530 000 in Pirkanmaa Health Care District, including the city of Tampere. In this area the treatment of rheumatic diseases with biologicals is confined to the Centre for Rheumatic Diseases, Tampere University Hospital. During 1999–2005 all of the patients (n=104) treated according to the national guidelines with infliximab as their first biological treatment for active RA or SpA in the Centre for Rheumatic Diseases were analysed in this study. In this study, the decision to start infliximab treatment was made by the discretion of an experienced rheumatologist, not as a randomized enrolment in a clinical trial, thereby providing data for the outcomes of infliximab treatment in everyday practice.

In Finland, rheumatologists commonly use combination DMARD therapy in the treatment of active RA, aiming to achieve remission (15). According to the national recommendations, infliximab treatment is used when patients have active RA despite combination DMARD therapy. Thus, very differently from randomized clinical trials, the patients analysed in this study had severe, refractory disease and ongoing treatment with combinations of DMARDs, glucocorticoids, and NSAIDs adjusted by their rheumatologist. In contrast to randomized clinical studies, different combinations of DMARDs (and not methotrexate alone) were used in addition to infliximab. Use of combinations of DMARDs, and severe and active RA or SpA, is associated with a high risk for adverse events and this must be taken into account when interpreting the results of the present study. In clinical studies, continuation rates of 82–91% with ACR20 criteria were reported by Maini et al after 7.5 months of treatment depending on the dose and infusion intervals (2), and 79% after 13.5 months of treatment reported by Lipsky et al (3). In observational studies, continuation rates seem to be somewhat lower than in randomized clinical trials, 82% continued infliximab infusions after 6 months' (7), 66% (6) and 85% (8) after 1 year's intervention. In the present study, 71% of the patients continued the medication after 6 months of treatment, i.e. they achieved at least 50% response without adverse events compelling discontinuation the treatment. Indeed, seven of 104 patients discontinued infliximab treatment due to remission defined on clinical grounds. In the present study the continuation rate was 68% in RA patients and 76% in SpA patients. Although the difference was small, it is in line with a Spanish report, where SpA patients had 33% lower probability of discontinuing the biologicals than RA patients (16). In some clinical trials, infliximab has been given at higher doses and/or shorter intervals to patients with SpA than to patients with RA (4). In the present study, infliximab treatment was started at a dose of 3 mg/kg in SpA patients as well, and, if needed, the dose was increased and/or the infusion interval adjusted along the response. In accordance with this, Braun et al concluded in their review that that dose is often also adequate in SpA patients (4).

Response to infliximab treatment is usually evident after 2 weeks of treatment, when over 50% of the RA

patients have been reported to achieve ACR20 response (2). Eight patients (27% of discontinuers, 8% of all patients) in our study did not achieve our continuation criteria (ACR50 or BASDAI > 50%/2 cm), and they discontinued the medication after 4 months of treatment. This finding is in accordance with previous studies, where about 10% discontinuation rates due to inefficacy have been reported in observational studies (6, 8). Lipsky et al (3) reported 12% discontinuation rates due to inefficacy in their clinical study. It is worth noting that continuation criteria in the above-mentioned studies have been mostly ACR20 and not ACR50 as in the present study and in clinical practice in Finland. In patients who responded to the infliximab treatment and continued the treatment, the glucocorticoid dose was decreased by 40%. There was no change in the number of concomitant DMARDs during the 6 months' follow-up among continuers. In support of this, Nordström et al recently reported that the median dose of glucocorticoids was reduced from 7.5 mg to 5 mg after 3 months of treatment with biologicals but there were no major changes in the use of concomitant DMARDs (17).

There is an increased risk for infections in RA (18, 19) and the use of conventional DMARDs further increases the risk (20). The use of TNFα antagonists amplifies the risk for infections (9). Lung, skin, soft tissue, joint, and bone infections are the most frequently reported severe infections during infliximab treatment and serious generalized infections are slightly more probable in RA patients treated with biological agents than in those treated with conventional DMARDs (9–11). In randomized clinical trials, 9–20% rates of severe adverse events have been reported, depending on the dose and infusion frequency of infliximab and the concomitant DMARDs (2, 3). Most of the patients in the present study (95%) had at least one DMARD in addition to infliximab treatment. Only those adverse events that led to discontinuation of infliximab treatment were registered, and they often required either medical treatment or hospitalization. In the present study, 13% of all patients were compelled to discontinue the medication due to adverse events. Infection was the most common adverse event reported (46% of adverse events). Three pneumonias, one septic arthritis, one soft tissue infection (gluteal abscess), and one generalized infection were registered during the follow-up. Infections are more common in elderly RA patients and in patients with severe disease history (21). Accordingly, patients with adverse events leading to discontinuation of treatment in this study were older (mean age 53 years) and had longer disease duration (17 years) than the other patients who discontinued the treatment (mean age 47 years, 12 years disease duration). Increased risk of tuberculosis is associated with infliximab treatment (22, 23) and in Finland tuberculosis is routinely screened prior to the commencement of infliximab treatment according to the national guidelines. In the present study, there was one case of tuberculosis, which was successfully treated with antimicrobial drugs. In Finland, the incidence of new and relapsed cases of tuberculosis is very low, with only six cases/100 000 people in 2004 (24), compared with the incidence in Europe of 50 cases/100 000 people (25).

Hypersensitivity reactions associated with infliximab treatment are fairly common, but rarely life-threatening. According to Wasserman et al, 2.7% of patients discontinued infliximab treatment due to hypersensitivity reactions and they most frequently occurred during the third or fourth infusion (12), while in the study by Maini et al, hypersensitivity reactions were most common during the first infusion (2). In our study, 5% of patients discontinued infliximab treatment due to hypersensitivity reactions, which occurred during/after the fourth to fifth infusion. Similarly, as in the study of Wasserman et al (12), we found that urticaria, rash, itching, and dyspnoea were the most frequently reported symptoms. Four out of five hypersensitivity reactions appeared during the infusion and one delayed reaction occurred a few days after the infusion.

Elevated aminotransferases in one patient and one case of cytopaenia were reported in our study. Recently, Konttinen et al reported 21 cases of elevated aminotransferases and four patients with leucopaenias (26) in their analysis of 248 patients with adverse events during TNFα antagonist treatment. Previously, only a few separate cases of leucopaenias had been reported (7, 27–29). One case of elevated aminotransferases associated with autoimmune hepatitis during infliximab treatment has been reported (30). Mildly or moderately elevated liver enzymes have been described, especially in SpA patients, during infliximab treatment (4), and van der Hejde et al (5) reported in their clinical study an elevation of liver enzymes in 5.9% patients, but there were no discontinuations of the infliximab treatment because of elevated liver enzymes. In this study there were no cases of malignancy, congestive heart failure, or neurological disorder, although they have been associated with anti-TNF antibody therapies in previous studies (31, 32).

In the present study, patients treated with infliximab had severe, refractory disease despite ongoing treatment with combinations of DMARDs. Seventy-eight per cent of the patients achieved at least a 50% response when infliximab was added to the treatment. Incidence of infections and hypersensitivity reactions as adverse events were in line with previous reports. Two rare, drug-related adverse events were reported, one patient with leucopaenia and one patient with elevated aminotransferases.

Acknowledgements

We thank Heli Määttä and Heli Pikkuharju for excellent secretarial help. We also thank the clinical rheumatologists and the staff in the Centre for Rheumatic Diseases, Tampere University Hospital for their help in this study. The study was supported by Clinical Drug Research Graduate School, Finland and the Competitive Research Funding of the Pirkanmaa Hospital District, Finland.

References

1. Feldmann M, Maini RN. Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? Annu Rev Immunol 2001;19:163–96.
2. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. 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 1999;354:1932–9.
3. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000;343:1594–602.
4. Braun J, Baraliakos X, Brandt J, Sieper J. Therapy of ankylosing spondylitis. Part II: Biological therapies in the spondyloarthritides. Scand J Rheumatol 2005;34:178–90.
5. van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582–91.
6. Flendrie M, Creemers MC, Welsing PM, den Broeder AA, van Riel PL. Survival during treatment with tumour necrosis factor blocking agents in rheumatoid arthritis. Ann Rheum Dis 2003;62(Suppl 2):ii30–3.
7. Wendling D, Materne GE, Michel F, Lohse A, Lehuede G, Toussirot E, et al. Infliximab continuation rates in patients with rheumatoid arthritis in everyday practice. Joint Bone Spine 2005;72:309–12.
8. Voulgari PV, Alamanos Y, Nikas SN, Bougias DV, Temekonidis TI, Drosos AA. Infliximab therapy in established rheumatoid arthritis: an observational study. Am J Med 2005;118:515–20.
9. Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum 2005;52:3403–12.
10. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006;54:2368–76.
11. Salliot C, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S, et al. Infections during tumour necrosis factor-{alpha} blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology (Oxford).
12. Wasserman MJ, Weber DA, Guthrie JA, Bykerk VP, Lee P, Keystone EC. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. J Rheumatol 2004;31:1912–17.
13. [Working group set by Finnish Medical Society Duodecim and Finnish Society for Rheumatology, Helsinki, Finland. Rheumatoid arthritis Current Care Guideline (update June 2003). Finland Medical Society Duodecim], in Finnish (www.kaypahoito.fi).
14. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.
15. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila 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.
16. Carmona L, Gomez-Reino JJ; BIOBADASER Group. Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis. Data from the Spanish registry BIOBADASER. Arthritis Res Ther 2006;8:R72.
17. Nordstrom DC, Konttinen L, Korpela M, Tiippana-Kinnunen T, Eklund K, Forsberg S, et al. Classic disease modifying anti-rheumatic drugs (DMARDs) in combination with infliximab. The Finnish experience. Rheumatol Int 2005:1–8.
18. Mutru O, Laakso M, Isomaki H, Koota K. Ten year mortality and causes of death in patients with rheumatoid arthritis. Br Med J (Clin Res Ed) 1985;290:1797–9.
19. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002;46:2294–300.
20. Capell HA. Disease modifying antirheumatic drugs: long-term safety issues. J Rheumatol Suppl 2001;62:10–15.
21. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002;46:2287–93.
22. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001;345:1098–104.
23. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD; BIOBADASER Group. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum 2003;48:2122–7.
24. World Health Organization, Tuberculosis country profile/Finland (www.who.int/globalatlas/dataQuery/default.asp).
25. World Health Organization, Tuberculosis: infection and transmission (www.who.int/mediacentre/factsheets/fs104/en/index.html#global).
26. Konttinen L, Honkanen V, Uotila T, Pollanen J, Waahtera M, Romu M, et al. Biological treatment in rheumatic diseases: results from a longitudinal surveillance: adverse events. Rheumatol Int 2006;26:916–22.
27. Vidal F, Fontova R, Richart C. Severe neutropenia and thrombocytopenia associated with infliximab. Ann Intern Med 2003;139:W–63.
28. Favalli EG, Varenna M, Sinigaglia L. Drug-induced agranulocytosis during treatment with infliximab in enteropathic spondyloarthropathy. Clin Exp Rheumatol 2005;23:247–50.
29. Montane E, Salles M, Barriocanal A, Riera E, Costa J, Tena X. Antitumor necrosis factor-induced neutropenia: a case report with double positive rechallenges. Clin Rheumatol 2007;26:1527–9.
30. Germano V, Picchianti Diamanti A, Baccano G, Natale E, Onetti Muda A, et al. Autoimmune hepatitis associated with infliximab in a patient with psoriatic arthritis. Ann Rheum Dis 2005;64:1519–20.
31. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. J Am Med Assoc 2006;295:2275–85.
32. Hyrich KL, Silman AJ, Watson KD, Symmons DP. Anti-tumour necrosis factor alpha therapy in rheumatoid arthritis: an update on safety. Ann Rheum Dis 2004;63:1538–43.

Rheumatol Int (2008) 28:261–269
DOI 10.1007/s00296-007-0436-0

ORIGINAL ARTICLE

Etanercept and adalimumab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: adverse events and other reasons leading to discontinuation of the treatment

Tiina Levälampi · Markku Korpela · Katriina Vuolteenaho · Eeva Moilanen

Received: 30 June 2007 / Accepted: 23 July 2007 / Published online: 6 September 2007

Abstract In the present study, we determined from a single-center data the treatment continuation, discontinuation and reasons for discontinuation in the patients with active rheumatoid arthritis (RA) or spondyloarthropathies (SpA) who were treated with etanercept or adalimumab. All RA and SpA patients, who were treated with etanercept ($n = 53$) or adalimumab ($n = 43$) as their first biological treatment according to national guidelines in the Center for Rheumatic Diseases, Tampere University Hospital during the years 1999–2005, were analyzed at baseline and after 1-year treatment. The treatment was regarded ineffective if the clinical response was lower than ACR50 in RA or the reduction of BASDAI was lower than 50% or 2 cm in SpA. After 1 year, the continuation rate was 74% with etanercept and 60% with adalimumab. Mean prednisolone dose among continuers was diminished by 52% in etanercept-treated patients and by 44% in adalimumab-treated patients. During 1-year follow-up, 14 (26%) of the etanercept-treated patients and 17 (40%) of the adalimumab-treated patients discontinued the medication. Eleven patients were regarded as poor responders, seven in etanercept group and four in adalimumab group. Adverse events (mainly infections and injection reactions) caused six discontinuations in etanercept-treated group and 11 discontinuations in adalimumab-treated group. Etanercept was discontinued due to other adverse event in two patients: in one patient due to adenocarcinoma of ovary and in one patient due to drug-related leukopenia. One patient treated with adalimumab developed clinical and immunological features of systemic lupus erythematosus (SLE). In the present study, etanercept and adalimumab treatments were started in patients who had active RA or SpA despite ongoing treatment with combinations of traditional disease modifying antirheumatic drugs (DMARDs). Thirty-nine (74%) patients and twenty-six (60%) patients achieved at least 50% response when etanercept or adalimumab was added to their earlier DMARD treatment. Adverse events (mainly infections and injection reactions) were in line with previous reports. Three rare adverse events were reported: one patient with ovarial carcinoma, one with leukopenia and one with features of drug-induced SLE.

Keywords Etanercept · Adalimumab · Rheumatoid arthritis · Spondyloarthropathies · Adverse events

T. Levälampi · K. Vuolteenaho · E. Moilanen (✉)
The Immunopharmacology Research Group,
Medical School, University of Tampere and Research Unit,
Tampere University Hospital, 33014 Tampere, Finland
e-mail: eeva.moilanen@uta.fi

M. Korpela
Center for Rheumatic Diseases,
Tampere University Hospital, Tampere, Finland

Introduction

Tumor necrosis factor alpha (TNFα) modulators etanercept and adalimumab have proved to be effective and well tolerated in the treatment of rheumatoid arthritis [1–4] and spondyloarthropathies [5]. They have established their place in the everyday practice when traditional disease modifying antirheumatic drugs (DMARDs) are not effective enough. Although etanercept and adalimumab are generally well tolerated, there are complications and discontinuations of the treatment due to adverse events [1–4, 6], mainly infections [7–9] and injection site reactions [1–4].

In the present study, we evaluated clinical practice outcomes of etanercept and adalimumab treatments in

comparison with prospective randomized clinical studies. Previous reports using ACR response criteria usually prefer ACR20 as the criteria for continuation of etanercept and adalimumab treatment, while in Finland the criteria for continuation has been set as ACR50 or a better response [10]. According to the national guidelines [10], treatment with TNFα antagonists is indicated if the patient is suffering from continuously active disease despite the treatment with combinations of traditional DMARDs, including methotrexate. In addition, TNFα antagonist is usually added to the treatment with one or more DMARDs (see Sect. "Patients and methods"). In the present study, we analyzed single rheumatological center data of all patients with RA or SpA, who received etanercept or adalimumab as their first biological treatment on clinical grounds according to the national guidelines. We were also interested in the safety and the outcome of etanercept or adalimumab treatment in combination with DMARDs. We defined the number of patients who achieved at least 50% response and continued the treatment with etanercept or adalimumab, the number of patients who discontinued the treatment and the reason for discontinuation and evaluated in more detail the adverse events leading to discontinuation of the treatment.

Patients and methods

In the present study, all patients with active rheumatoid arthritis or spondyloarthropathies were treated with etanercept or adalimumab as their first biological treatment during the years 1999–2005, in the Center for Rheumatic Diseases at the Tampere University Hospital, Finland. According to national recommendations, the criteria to start TNFα antagonist treatment for rheumatoid arthritis was that the patient should be suffering from continuously active RA [at least six swollen and tender joints, and additionally the duration of morning stiffness should be at least 45 min and/or erythrocyte sedimentation rate (ESR) $\geq$ 30 mmHg and/or serum C-reactive protein (CRP) $\geq$ 28 mg/l] despite treatment with combinations of traditional DMARDs including methotrexate and low-dose glucocorticoids [10]. The criteria to start biologicals for the treatment of ankylosing spondylitis were: (1) ineffectiveness of at least two nonsteroidal anti-inflammatory drugs (NSAIDs) for at least 3 months, (2) sulphasalazine (methotrexate if sulphasalazine is contraindicated) or possibly if other DMARDs had proved ineffective, and (3) the patient had an active disease based on BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) (¸4 cm) and on clinical grounds [acute sacroiliitis, elevated acute phase reactants, magnetic resonance imaging (MRI) Wndings]. In other spondyloarthropathies like psoriatic arthritis (PsA) or inXammatory bowel disease (IBD) associated arthritis, there were no deWned criteria to start treatment with biologicals, but the decision was made on clinical grounds by an experienced rheumatologist based on the severity of oligo/polyarthritis and inXammatory axial disease, and criteria available for rheumatoid arthritis and ankylosing spondylitis.

Etanercept was given subcutaneously with a dose of 25 mg twice a week and adalimumab with a dose of 40 mg every other week subcutaneously. Etanercept or adalimumab was usually combined with methotrexate and possibly with other DMARDs (mostly sulphasalazine or hydroxychloroquine) and small-dose prednisolone. The clinical response was carefully followed and registered by an experienced rheumatologist at each visit. In RA, the evaluation included ACR (American College of Rheumatology) response criteria [11] including the number of swollen and tender joints, the physician's assessment of disease activity (VAS, Visual Analog Scale, 0–10 cm), patient's assessment of general health (VAS), pain (VAS) and HAQ (Health Assessment Questionnaire), and markers of acute phase activity (ESR and CRP). The treatment response lower than ACR50 was regarded ineffective. In spondyloarthropathies, the clinical response included BASDAI and BASFI (Bath Ankylosing Spondylitis Functional Index) indexes, and the treatment was regarded ineffective if the reduction of BASDAI index was lower than 50% or less than 2 cm.

Concomitant drug treatment including glucocorticoids, DMARDs and NSAIDs, was documented. The reason of withdrawal (adverse event, inefficiency, and other reasons) was registered and in the case of an adverse event, discrete stationary was filled in.

Results

Patients

Patients were treated in the Center for Rheumatic Diseases, Tampere University Hospital during the years 1999–2005. The survey included all RA and SpA patients (n = 96) who had severe and active diseases despite effective antirheumatic drug treatment, and who started etanercept or adalimumab, as their first biological treatment. In the national guidelines the criterion to start treatment with TNFα antagonist is that the patient suffers from a severe and refractory disease despite active antirheumatic treatment. TNFα antagonist is usually added to the combination of one or more DMARDs. We analyzed the patterns of drug continuation, discontinuation and reasons for discontinuation in patients treated with etanercept or adalimumab.

Etanercept

Etanercept was commenced as the first biological treatment in 53 RA and SpA patients (Table 1). At the beginning of the treatment the mean age of the patients was 44 (range 18–75) years, 58% (31 patients) were females and mean disease duration was 10 (range 1-36) years. Concomitant DMARDs in addition to etanercept was used in 94% of the patients and 81% used glucocorticoids. Thirty-one (58%) patients had rheumatoid arthritis including seropositive RA in 21, seronegative RA in 5 and juvenile idiopathic arthritis (JIA) in 5 patients (Table 2). Twenty-two (42%) of the 53 patients had spondyloarthropathy (SpA) including ankylosing spondylitis (AS) in 10 and psoriatic arthritis (PsA) in 5 patients. Seronegative oligoarthritis, reactive arthritis and sacroiliitis were represented in a minor part (Table 2).

The follow-up data were assessed after the 1-year etanercept treatment (Tables 1, 2). Thirty-nine (74%) patients achieved at least 50% improvement and continued the medication after 1 year. During the first year 14 (26%) of etanercept-treated patients discontinued the medication (Table 3). Half of the patients (seven patients) did not achieve 50% improvement in clinical parameters and discontinued the treatment due to poor response. Six patients experienced an adverse event during the 1-year follow-up leading to discontinuation of the treatment and one patient discontinued due to pregnancy.

Among the patients who continued the etanercept treatment after 1 year, the proportion of the patients using glucocorticoid treatment had diminished by 30%. The mean glucocorticoid dose decreased by 52%, from 6.0 ± 0.7 to 2.9 ± 0.5 mg/day (mean $\pm$ SEM, $P < 0.0001$) among continuers. The number of concomitant DMARDs reduced along successful etanercept treatment; after 1 year, 25% of the patients had no concomitant DMARD and 47% used only one DMARD (Table 1).

All the six adverse events appearing during the 1-year follow-up and leading to discontinuation of the treatment were defined more precisely (Table 4). Five of the adverse events occurred during the first 6 months and one, after 9 months' etanercept treatment (Fig. 1a). There was one serious infection (generalized and recurrent herpes infection), three injection reactions and two other adverse events.

Generalized and recurrent herpes infection in a 26-year-old woman caused discontinuation of the etanercept treatment after 5 months. Three injection reactions occurred during the first year after the initiation of etanercept treatment. One patient suffered from irritation at injection site after 1-month etanercept treatment and another patient had congestion of throat, headache and tingle of lower limbs after 6 weeks' treatment. The third patient developed vesicles in mouth and genitals, which were not considered herpetic according to the treating gynecologists, and etanercept was discontinued after 6 months from the commencement of the treatment.

Table 1 Characteristics of patients treated with etanercept

	At the beginning	After 1 year of etanercept treatment	
	($n = 53$)	Continued ($n = 39$)	Discontinued ($n = 14$)
Age, years, mean (range)	44 (18–75)	44 (19–76)	44 (26–61)
Female (%)	58	53	67
Disease duration, years, mean (range)	10 (1–36)	13 (3–37)	7 (1–22)
Number of concomitant DMARDs			
0 (%)	6	25	17
1 (%)	22	47	17
2 (%)	36	20	50
3 or more (%)	36	8	17
Glucocorticoid intake (%)	81	52	83
Glucocorticoid dosage, mean (mg/day)	6.8	2.9	5.4

DMARD disease modifying antirheumatic drug

Table 2 Etanercept-treated patients according to their diagnosis

Diagnosis	At the beginning, $n = 53$	Continuing after 1 year, $n = 39$ (74%)	
	n	*n*	(%)
RA	31	23	74
Seropositive rheumatoid arthritis	21	15	71
Seronegative rheumatoid arthritis	5	4	80
Juvenile idiopathic arthritis	5	4	80
SpA	22	16	73
Ankylosing spondylitis	10	8	80
Psoriatic arthritis	5	5	100
Seronegative oligoarthritis	4	2	50
Sacroiliitis	2	0	0
Reactive arthritis	1	1	100

RA rheumatoid arthritis, *SpA* spondyloarthropathy

Table 3 Reasons to discontinue etanercept treatment

Reason	Number	(%)
Lack of efficacy	7	50
Adverse event	6	43
Other reason	1	7
Total	14	100

Table 4 Adverse events leading to discontinuation of etanercept treatment during the first year

Classification	Number	Diagnosis	Age (years)	Sex	Disease duration (years)	DMARD's	Time of adverse event (months)	Adverse event
Infection	1	Juvenile idiopathic arthritis	26	M	19	PRED 5 mg/day MTX 20 mg/week HCQ 300 mg/day	5	Recurrent generalized herpes
Injection reaction	1	Seropositive rheumatoid arthritis	34	F	3	PRED 7.5 mg/day	1	Redness, itching and irritation of the injection site
	2	Seronegative oligoarthritis	43	F	7	PRED 5 mg/day MTX 25 mg/week SSZ 2,000 mg/day	1.5	Tingle and numbness of lower limbs, congestion of throat, and headache
	3	Seronegative rheumatoid arthritis	43	F	14	PRED 20 mg/day LEF 150 mg/day HCQ 300 mg/day	6	Vesicles in mouth and genitals, and itch of skin
Other adverse event	1	Sacroiliitis	37	F	1	MTX 20 mg/week SSZ 2,000 mg/day	6	Leukopenia: leukocytes 3.1×10^9/l and polymorphonuclear leukocytes 1.16×10^9/l
	2	Seropositive rheumatoid arthritis	61	F	4	PRED 2.5 mg/day MTX 25 mg/week SSZ 2,000 mg/day HCQ 300 mg/day	9	Mucous adenocarcinoma of ovary with abdominal metastasis

DMARD disease modifying antirheumatic drug, *HCQ* hydroxychloroquine, *LEF* leflunomide, *MTX* methotrexate, *PRED* prednisolone, *SSZ* sulfasalazine

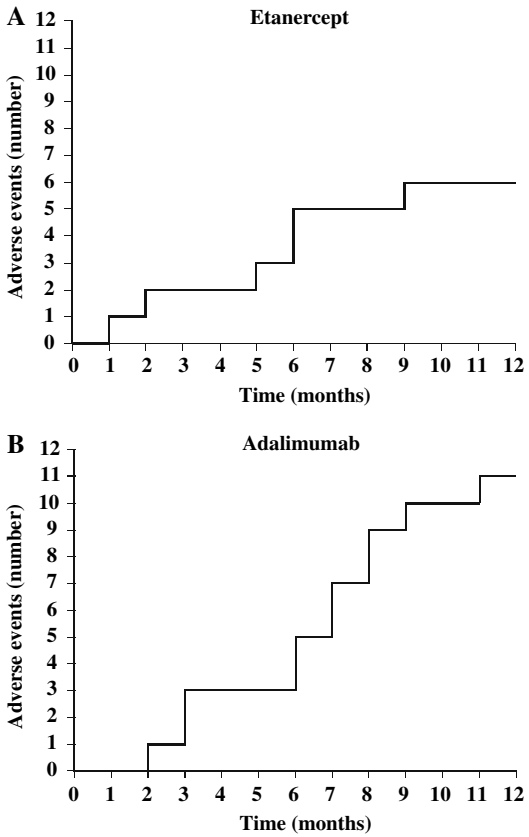

Fig. 1 The cumulative number of the adverse events that led to discontinuation of the treatment during 1-year etanercept (**a**) and adalimumab (**b**) treatment

Two patients had to discontinue etanercept treatment due to other adverse events. One patient developed leukopenia (leukocytes 3.1×10^9/l), which did not mitigate after discontinuation of the concomitant methotrexate and sulfasalazine. After discontinuation of etanercept the leukocyte levels were normalized. In another patient, a 61-year-old woman, mucous adenocarcinoma of the ovary with metastasis was observed during etanercept treatment.

Adalimumab

Forty-three patients with RA or SpA started adalimumab as their first biological treatment (Table 5). The mean age at the beginning of the treatment was 52 (range 17–74) years, 72% of the patients were females and the mean duration of the disease was 16 (range 1–45) years. Most of the patients (93%) used at least one concomitant DMARD and 93% of them used also oral glucocorticoids. The patient characteristics are shown in Table 5. Forty patients (93%) had rheumatoid arthritis and three-quarters of them had seropositive disease. Fourteen percent of the patients had seronegative rheumatoid arthritis and 9% had juvenile idiopathic arthritis. Three patients (7%) had spondyloarthropathy (Table 6).

The follow-up data was assessed after 1-year adalimumab treatment (Tables 5, 6). Sixty percent of the patients (26 patients) achieved 50% response and continued adalimumab treatment. During the 1-year follow-up 17 (40%) patients discontinued the medication. Four (23%) of

Table 5 Characteristics of patients treated with adalimumab

	At the beginning	After 1 year of adalimumab treatment	
	(n = 43)	Continued (n = 26)	Discontinued (n = 17)
Age, years, mean (range)	52 (17–74)	50 (24–70)	56(17–74)
Female (%)	72	73	76
Disease duration, years, mean (range)	16 (1–45)	16 (2–34)	17 (1–45)
Number of concomitant DMARDs			
0 (%)	7	8	18
1 (%)	32	58	41
2 (%)	26	31	12
3 or more (%)	35	4	29
Glucocorticoid intake (%)	93	73	100
Glucocorticoid dosage, mean (mg/day)	7.4	3.6	8.1

DMARD disease modifying antirheumatic drug

Table 6 Adalimumab-treated patients according to their diagnosis

Diagnosis	At the beginning, n = 43	Continuing after 1 year, n = 26 (60%)	
	n	n	(%)
RA	40	23	58
Seropositive rheumatoid arthritis	30	15	50
Seronegative rheumatoid arthritis	6	4	67
Juvenile idiopathic arthritis	4	4	100
SpA	3	3	100
Seronegative oligoarthritis	3	3	100

RA rheumatoid arthritis, *SpA* spondyloarthropathy

the patients who discontinued adalimumab did not achieve 50% improvement and discontinued due to poor response. Adverse events leading to discontinuation of the treatment during the first year of adalimumab treatment appeared in 11 (26%) patients. Two patients discontinued adalimumab treatment due to other reasons, one patient discontinued voluntarily and the other patient due to changes in the chest radiology, which were regarded not to be related to adalimumab treatment (Table 7).

During the 1-year adalimumab treatment the proportion of the patients with concomitant DMARD treatment decreased, especially the proportion of the patients with three or more concomitant DMARD diminished from 35 to 4%. The use of glucocorticoids was more prevalent at the beginning of the adalimumab treatment and decreased during the 1-year follow-up from 93 to 73%. Mean prednisolone dose decreased by 44% among the continuers from 6.2 ± 0.65 (mean ± SEM) to 3.5 ± 0.58 mg/day (P = 0.0008) (Table 5).

Table 7 Reasons to discontinue adalimumab treatment

Reason	Number	(%)
Lack of efficacy	4	23
Adverse event	11	65
Other reason	2	12
Total	17	100

We defined all 11 adverse events that led to discontinuation of adalimumab treatment during the first year of follow-up in more detail (Table 8). Three adverse events occurred after 2 or 3 months' treatment, but most of the adverse events (in eight patients) occurred after 6 months' treatment or later (Fig. 1b). Fifty-five percent (6/11) of the adverse events were infections. Three of the six infections were recurrent infections: one patient with recurrent dermatitis and urinary tract infections with fever, one patient with recurrent maxillary sinusitis and otitis media and one patient with recurrent urinary tract infections. Two patients suffered from persistent infections; one patient had infectious ulcer of the toe and the other patient had Herpes Zoster infection in the left part of the chest. One patient developed tinea of the palms.

Three of the eleven adverse events leading to discontinuation of the treatment were injection reactions. One patient had a local injection site reaction after 8 months' treatment. A 67-year-old woman had a skin reaction in the legs after 2 months' adalimumab treatment diagnosed by dermatologist as a purpura. Another patient had sickliness and intense headache after fourth and fifth injections.

Two patients had other adverse events leading to discontinuation of the treatment. One patient had intense sweating and insomnia and adalimumab was discontinued after 9 months of treatment. In a 33-year-old female, adalimumab treatment was stopped due to suspicion of mild SLE [rash, elevated serum DNA-antibodies (297 titer) and lowered levels of the complement components C3 (0.45 g/l) and C4 (0.04 g/l)].

Discussion

Tampere University Hospital provides specialist care for a population of about 500.000 in Pirkanmaa Health Care District including city of Tampere. In this area, the treatment of rheumatic diseases with TNFα antagonists is confined to the Center for Rheumatic Diseases, Tampere University Hospital. All patients (n = 96), treated according to national guidelines with etanercept or adalimumab as their first biological treatment for active RA or SpA in the Center for

Table 8 Adverse events leading to discontinuation of adalimumab treatment during the first year

Classification	Number	Diagnosis	Age (years)	Sex	Disease duration (years)	DMARD's	Time of adverse event (months)	Adverse event
Infection	1	Seropositive rheumatoid arthritis	49	M	14	PRED 10 mg/day MTX 25 mg/week	8	Recurrent infections (sinusitis)
	2	Seronegative rheumatoid arthritis	54	F	9	PRED 10 mg/day	11	Eczema of the hands with vesicles, diagnosed by dermatologist as tinea
	3	Seropositive rheumatoid arthritis	54	F	15	PRED 5 mg/day MTX 25 mg/week SSZ 2,000 mg/day	6	Herpes Zoster infection of the left part of the upper body
	4	Seropositive rheumatoid arthritis	59	F	29	PRED 5 mg/day	7	Recurrent infections (urinary tract infections)
	5	Seropositive rheumatoid arthritis	61	F	5	PRED 5 mg/day LEF 20 mg/day	6	Recurrent infections (dermatitis and urinary tract infection with fever)
	6	Seropositive rheumatoid arthritis	64	M	11	PRED 5 mg/day LEF 20 mg/day SSZ 2,000 mg/day HCQ 300 mg/day	3	Infectious ulcer of the toe
Injection reaction	1	Seronegative rheumatoid arthritis	53	F	7	PRED 15 mg/day MTX 15 mg/week SSZ 2,000 mg/day HCQ 300 mg/day	8	Local injection reaction
	2	Seropositive rheumatoid arthritis	67	F	45	PRED 7.5 mg/day HCQ 300 mg/day	2	Purple eczema of lower limbs
	3	Seropositive rheumatoid arthritis	74	F	13	PRED 12.5 mg/day LEF 20 mg/day	3	Sickliness, tingling and numbness after fourth injection, after fifth injection intense headache
Other adverse event	1	Seropositive rheumatoid arthritis	33	F	10	PRED 7.5 mg/day MTX 25 mg/week HCQ 257 mg/day	7	Suspicion of mild SLE: rash, elevated DNA-antibodies (ad 297 titer) and decreased complement levels (C3 0.45 and C4 0.04 g/l)
	2	Seropositive rheumatoid arthritis	61	F	20	PRED 5 mg/day	9	Insomnia and intense sweating, but also irregular injections

DMARD disease modifying antirheumatic drug, *HCQ* hydroxychloroquine, *LEF* leflunomide, *MTX* methotrexate, *PRED* prednisolone, *SSZ* sulfasalazine

Rheumatic Diseases during the years 1999–2005, were analyzed in the present survey. The decision to start treatment with either etanercept or adalimumab was made at the discretion of an experienced rheumatologist, not as a randomized enrolment in a clinical trial, and analysis of the patient records offers data of the outcomes of etanercept and adalimumab treatment in everyday practice.

In Finland, rheumatologists use commonly combination DMARD therapy in the treatment of active RA aiming to achieve remission [12]. According to the national recommendations, TNFα antagonist treatment is started if the patient has active RA or SpA despite of combination DMARD therapy. Contrary to randomized, controlled trials, the patients analyzed in the present study had severe, refractory disease and ongoing treatment with combinations of DMARDs, glucocorticoids and NSAIDs, adjusted by their rheumatologist. In the present study, the patients used different combinations of DMARDs in addition to etanercept or adalimumab, and not only MTX which has been the case in most randomized clinical trials of TNFα antagonists.

Loss of patients has been reported quite extensively, especially in observational studies [13, 14]. In the present study we were able to retrieve patient stationeries from all patients who started the treatment with etanercept or adalimumab, and there was no loss of patients during the follow-up. Kristensen et al. [15] reported in their study a better adherence to TNFα antagonist treatment, when a concomitant DMARD was included in the therapy and this may have influenced the very good compliance to the treatment in the present study. Previous studies also have reported better response to combination therapy than to monotherapy [3, 16]. The use of combinations of DMARDs, as well as severe and active RA or SpA may be associated with a high risk of adverse events, and that should be taken into account when interpreting the results of the present study.

In previous clinical studies with etanercept, after 6 months of treatment with a dosage of 25 mg twice a week, 40% of the patients achieved ACR50 response as monotherapy [1] and 69% when combined with methotrexate after 13 months treatment [3]. In clinical trials with adalimumab, 22% of the patients receiving adalimumab as monotherapy at a dose of 40 mg every other week achieved ACR50 after 26 weeks [4] and 55% of the patients with concomitant methotrexate after 6 months of treatment [2]. In the above-mentioned clinical studies patients had failed to respond to treatment at least with one DMARD. In observational studies, the continuation rate of etanercept after 1 year has ranged from 69 to 87% and that of adalimumab from 73 to 83% [14, 17, 18]. In the present study, 74% of the patients treated with etanercept and 60% of the patients treated with adalimumab continued the medication after 1 year of treatment and achieved at least 50% relief without adverse events compelling them to discontinue the treatment. In etanercept group, patients with RA and SpA had about similar continuation rates, although Carmona et al. [19] reported a better treatment survival rate in patients with SpA and Brocq et al. [14] reported the same for patients with AS. Because of a relatively small number of SpA patients in the adalimumab group the continuation rates between different subgroups or different diagnoses cannot be compared in the present study.

Response to etanercept or adalimumab treatment is usually evident immediately after two weeks' treatment, when 32% of etanercept-treated [1] and 35% of adalimumab-treated [4] RA patients had achieved ACR20 response in previous clinical studies. Seven patients (50% of discontinuers, 13% of treatment group) in our study treated with etanercept did not achieve our continuation criteria (ACR50 or BASDAI > 50%/2 cm), and they discontinued the medication after 5 months' treatment. Four patients (23% of discontinuers, 9% of the treatment group) treated with adalimumab did not achieve our continuation criteria (ACR50 or BASDAI > 50%/2 cm), and they discontinued the medication after 6 months' treatment. These findings are in accordance with previous studies, where 10% [6] and 15% [13] of the patients discontinued etanercept due to inefficacy. Discontinuation rates of 11% [17] and 12% [6] due to inefficacy have been reported in observational studies with adalimumab. Clinical studies with etanercept and adalimumab monotherapy have shown 15% [1] and 18% [4] discontinuation rates, respectively, due to inefficacy, during 6-month follow-up. It is worth noticing that continuation criteria in the above-mentioned studies have been mostly ACR20 and not ACR50 as in the present study and in the clinical practice in Finland. In patients who responded to the etanercept and adalimumab treatment and continued the treatment, the mean glucocorticoid dose was diminished by about 52% among etanercept treatment continuers and by 44% among adalimumab treatment continuers. The number of concomitant DMARDs could be diminished during the 1-year follow-up among continuers in both treatment groups.

There is an increased risk for infections in RA [20, 21] and the use of conventional DMARDs increases it further [22]. The use of TNFα antagonists amplifies the risk for infections [7]. Severe lung, skin, soft tissue, joint and bone infections are the most frequently reported severe infections during etanercept and adalimumab treatment and serious generalized infections are slightly more probable in RA patients treated with biological agents than in those treated with conventional DMARDs [7–9]. In clinical trials, 11% [3] rate of severe adverse events has been reported in patients treated with etanercept monotherapy and 12% [4] and 21% [16] rates for adalimumab monotherapy. In combi-

nation therapy with methotrexate, 13% of the etanercept-treated patients [3] and 19% adalimumab-treated patients had severe adverse events [16]. Most of the patients in the present study (94% with etanercept and 93% with adalimumab) had at least one DMARD in addition to etanercept or adalimumab treatment. Only those adverse events that led to discontinuation of treatment with biologicals were registered, and they often required either medical treatment or hospitalization. In the present study, 11% of all patients treated with etanercept and 26% of all patients treated with adalimumab were compelled to discontinue the medication due to an adverse event. Infections were the most common adverse events reported among patients treated with adalimumab; 55% (six patients) of the adverse events leading to discontinuation of the treatment were infections (14% of all adalimumab-treated patients). In the case of etanercept only one case of adverse events leading to discontinuation of the treatment was infection. There are reports about different molecular effects for three TNFα antagonists and possible effect of this on infection risk [23–25], which may also contribute to the present results. Increased risk of skin and urinary tract infection has been associated with anti-TNFα treatment [7]. In the present study, one genital herpes infection was registered during the follow-up in a patient treated with etanercept and one patient treated with adalimumab had herpes infection in the left part of the chest. In adalimumab-treated patients also one recurrent sinusitis, two recurrent urinary tract infections, one tinea and one infectious ulcer were documented during the 1-year follow-up. There were no cases of tuberculosis, although increased risk of it has been associated with the treatment with biologicals [26].

Injection site reactions are quite common, but rarely life threatening adverse events associated with etanercept and adalimumab treatment [1–4]. According to Hyrich et al. [6], 0.3% patients discontinued TNFα antagonist treatment due to injection site reaction and they most frequently occurred during the first month of the treatment. In the present study, 6% of the patients discontinued etanercept and 7% of the patients discontinued adalimumab treatment due to injection reaction and the reactions occurred mainly during the first 6 months of treatment, except one reaction that occurred after 8 months of treatment. In clinical studies, about 50% injection site reaction rates have been reported with etanercept monotherapy [1, 3] and 23% with combination therapy [3]. Patients with adalimumab monotherapy had 10% injection site reaction rate [4] and 12% injection site reaction/pain rate with combination therapy [2].

In the present study, we found elevated DNA-antibodies and decreased complement levels and rash in one patient treated with adalimumab (i.e., SLE-type immunological alterations). Weinblatt et al. [2] reported patients with elevated DNA-antibodies, but no symptoms of SLE were developed. A single case of a patient with drug-induced SLE during adalimumab treatment has been reported [27]. In addition, one of our patients treated with etanercept, developed cytopenia during the 1-year follow-up. Hyrich et al. [6] reported 38 cases of cytopenias in 6,739 patients and Konttinen et al. [28] four patients with leukopenias in their analysis of 308 adverse events during TNFα antagonist treatment. The European Medicines Agency (EMEA) and the Committee for Proprietary Medicinal Products (CPMP) stated (October 3, 2000) that etanercept might cause leukopenia and that this should be taken into account when treating patients, although leukopenia is reported rarely. One malignant disease, ovarial adenocarcinoma, was diagnosed in an etanercept-treated patient in our patient material. Malignancies have been reported previously [14, 28, 29], but the causality to the drug treatment in the present and earlier reported cases remain open.

In the present study, patients treated with etanercept or adalimumab had severe, refractory disease despite of ongoing treatment with combinations of DMARDs. Thirty-nine patients (74%) treated with etanercept and 26 patients (60%) with adalimumab achieved at least 50% response when TNFα antagonist was added to their DMARD treatment. Incidence of infections and injection reactions as adverse events leading to discontinuation of the treatment were in line with previous reports. Three rare drug-related adverse events were reported during the follow-up. One patient with leukopenia and one with immunological features of SLE, were both treated with adalimumab. One patient in the etanercept-treated groups was diagnosed to have mucous adenocarcinoma of ovary. The results support the clinical view that combination of DMARDs and TNFα antagonists is an effective and relatively safe treatment for severe and refractory RA and SpA.

Acknowledgments We thank Mrs. Heli Määttä and Mrs. Heli Pikkuharju for excellent secretarial help. Clinical rheumatologists and the staff in the Center for Rheumatic Diseases, Tampere University Hospital, are gratefully acknowledged. The study was supported by Clinical Drug Research Graduate School, Finland and the competitive research funding of the Pirkanmaa Hospital District.

References

1. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, Weaver AL, Keystone EC, Furst DE, Mease PJ, Ruderman EM, Horwitz DA, Arkfeld DG, Garrison L, Burge DJ, Blosch CM, Lange ML, McDonnell ND, Weinblatt ME (1999) Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 130:478–486
2. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, Teoh LA, Fischkoff SA, Chartash EK (2003) Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in

patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 48:35–45
3. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Martin Mola E, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M, TEMPO (trial of etanercept, methotrexate with radiographic patient outcomes) study investigators (2004) Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 363:675–681
4. van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, Settas L, Bijlsma JW, Todesco S, Dougados M, Nash P, Emery P, Walter N, Kaul M, Fischkoff S, Kupper H (2004) Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 63:508–516
5. Braun J, Baraliakos X, Brandt J, Sieper J (2005) Therapy of ankylosing spondylitis. Part II: biological therapies in the spondyloarthritides. Scand J Rheumatol 34:178–190
6. Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ, British society for rheumatology biologics register (2007) Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum 56:13–20
7. Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, Gromnica-Ihle E, Antoni C, Herzer P, Kekow J, Schneider M, Zink A (2005) Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum 52:3403–3412
8. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP, British society for rheumatology biologics register (2006) Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 54:2368–2376
9. Salliot C, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S, Dougados M (2006) Infections during tumour necrosis factor-{alpha} blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology (Oxford)
10. Working group set by Finnish Medical Society Duodecim and Finnish Society for Rheumatology, Helsinki, Finland. (Updated 08.06.2003) Rheumatoid arthritis Current Care Guideline. Finnish Medical Society Duodecim. Available at http://www.kaypahoito.fi (in Finnish)
11. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, Katz LM, Lightfoot R Jr, Paulus H, Strand V (1995) American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 38:727–735
12. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M, Laasonen L, Julkunen H, Luukkainen R, Vuori K, Paimela L, Blafield H, Hakala M, Ilva K, Yli-Kerttula U, Puolakka K, Jarvinen P, Hakola M, Piirainen H, Ahonen J, Palvimaki I, Forsberg S, Koota K, Friman C (1999) Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 353:1568–1573
13. Feltelius N, Fored CM, Blomqvist P, Bertilsson L, Geborek P, Jacobsson LT, Lindblad S, Lysholm J, Rantapaa-Dahlqvist S, Saxne T, Klareskog L, ARTIS Group (2005) Results from a nationwide postmarketing cohort study of patients in Sweden treated with etanercept. Ann Rheum Dis 64:246–252
14. Brocq O, Roux CH, Albert C, Breuil V, Aknouche N, Ruitord S, Mousnier A, Euller-Ziegler L (2007) TNFalpha antagonist continuation rates in 442 patients with inflammatory joint disease. Joint Bone Spine 74:148–154
15. Kristensen LE, Saxne T, Nilsson JA, Geborek P (2006) Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther 8:R174
16. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL, 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
17. Flendrie M, Creemers MC, Welsing PM, den Broeder AA, van Riel PL (2003) Survival during treatment with tumour necrosis factor blocking agents in rheumatoid arthritis. Ann Rheum Dis 62(Suppl2):ii30–ii33
18. Zink A, Listing J, Kary S, Ramlau P, Stoyanova-Scholz M, Babinsky K, von Hinueber U, Gromnica-Ihle E, Wassenberg S, Antoni C, Herzer P, Kekow J, Schneider M, Rau R (2005) Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis 64:1274–1279
19. Carmona L, Gomez-Reino JJ, BIOBADASER Group (2006) Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis. Data from the Spanish registry BIOBADASER. Arthritis Res Ther 8:R72
20. Mutru O, Laakso M, Isomaki H, Koota K (1985) Ten year mortality and causes of death in patients with rheumatoid arthritis. Br Med J (Clin Res Ed) 290:1797–1799
21. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE (2002) Predictors of infection in rheumatoid arthritis. Arthritis Rheum 46:2294–2300
22. Capell HA (2001) Disease modifying antirheumatic drugs: long-term safety issues. J Rheumatol Suppl 62:10–15
23. Scallon B, Cai A, Solowski N, Rosenberg A, Song XY, Shealy D, Wagner C (2002) Binding and functional comparisons of two types of tumor necrosis factor antagonists. J Pharmacol Exp Ther 301:418–426
24. Nestorov I (2005) Clinical pharmacokinetics of tumor necrosis factor antagonists. J Rheumatol Suppl 74:13–18
25. Furst DE, Wallis R, Broder M, Beenhouwer DO (2006) Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. Semin Arthritis Rheum 36:159–167
26. Brassard P, Kezouh A, Suissa S (2006) Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis 43:717–722
27. van Rijthoven AW, Bijlsma JW, Canninga-van Dijk M, Derksen RH, van Roon JA (2006) Onset of systemic lupus erythematosus after conversion of infliximab to adalimumab treatment in rheumatoid arthritis with a pre-existing anti-dsDNA antibody level. Rheumatology 45:1317–1319
28. Konttinen L, Honkanen V, Uotila T, Pollanen J, Waahtera M, Romu M, Puolakka K, Vasala M, Karjalainen A, Luukkainen R, Nordstrom DC, for the ROB-FIN study group (2006) Biological treatment in rheumatic diseases: results from a longitudinal surveillance: adverse events. Rheumatol Int 26:916–922
29. Hyrich KL, Silman AJ, Watson KD, Symmons DP (2004) Anti-tumour necrosis factor alpha therapy in rheumatoid arthritis: an update on safety. Ann Rheum Dis 63:1538–1543

Rheumatol Int
DOI 10.1007/s00296-009-1203-1

ORIGINAL ARTICLE

Infliximab treatment in patients with rheumatoid arthritis and spondyloarthropathies in one rheumatological center: two years' drug survival

Tiina Levälampi · Markku Korpela · Katriina Vuolteenaho · Eeva Moilanen

Received: 2 July 2009 / Accepted: 13 September 2009

Abstract The aim of the present study was to determine the drug survival during 2 years' follow-up in patients ($n = 104$) with active rheumatoid arthritis (RA) or spondyloarthropathy (SpA) who were treated with infliximab as their first biological anti-rheumatic drug in a single rheumatological center. According to the national guidelines, infliximab was added to the treatment with combinations of traditional disease-modifying anti-rheumatic drugs (DMARD). Patients' records were analyzed at baseline and after 2 years of follow-up. The response to treatment was determined inadequate if the response was lower than ACR50 (American College of Rheumatology 50) in RA or the reduction of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was lower than 50% or 2 cm in SpA. Drug survival in infliximab-treated patients after 2 years was 40%, and among those who continued with the therapy the prednisolone dose has been reduced by 52%. Discontinuation rate was 60% during 2 years of follow-up, where 7% achieved remission and 22% of the patients were regarded as poor responders. As much as 24% of the patients discontinued due to an adverse event, mainly infections and hypersensitivity reactions. Two drug-related leukopenias were diagnosed. In the present study, infliximab therapy was initiated in RA or SpA patients who had active disease despite ongoing treatment with combinations of DMARDs. The drug survival with infliximab was 40% after 2 years of follow-up. During the 2-year follow-up, 60% discontinued infliximab treatment, mainly due to unsatisfactory or waning efficacy or a severe adverse event.

Keywords Infliximab · Rheumatoid arthritis · Spondyloarthropathies · Adverse events

T. Levälampi · K. Vuolteenaho · E. Moilanen (✉)
The Immunopharmacology Research Group,
Medical School, University of Tampere and Research Unit,
Tampere University Hospital, 33014 Tampere, Finland
e-mail: eeva.moilanen@uta.fi

T. Levälampi
e-mail: tiina.levalampi@uta.fi

K. Vuolteenaho
e-mail: katriina.vuolteenaho@uta.fi

M. Korpela
Deparment of Internal Medicine, Center for Rheumatic Diseases,
Tampere University Hospital, Tampere, Finland
e-mail: markku.korpela@pshp.fi

Introduction

Tumor necrosis factor alpha (TNFα) modulator infliximab has been shown to be effective, antierosive and well tolerated in the treatment of rheumatoid arthritis (RA) [1–4] and spondyloarthropathies (SpA) [5, 6] in clinical trials. It is routinely used in the everyday practice when traditional DMARDs are not sufficiently effective. Although infliximab is generally safe and well tolerated, sometimes the treatment must be discontinued due to adverse events [1–3, 6–10], mainly infections [11–14] and hypersensitivity reactions [14, 15]. In addition, inadequate or waning efficacy complicates drug survival in infliximab-treated patients [8, 10, 14, 16].

Many clinical trials use ACR20 as the criteria for continuation of infliximab treatment, while in Finland the criteria for continuation has been set as ACR50 or a better response [17]. According to the national guidelines [17], TNFα antagonist treatment is indicated if the patient suffers from continuously active disease despite the treatment with combinations of traditional disease-modifying antirheumatic drugs (DMARD), including methotrexate. In addition, a TNFα antagonist is usually added to the treatment with one

Published online: 10 October 2009

or more DMARDs (see "Patients and methods"). In the present study, our interest was to analyze data from patients with active and refractory RA or SpA in a single rheumatological center, who received infliximab as their first biological treatment in combination with DMARDs on clinical grounds according to the national guidelines. We have recently published a 6 months' follow-up data, on RA and SpA patients receiving infliximab as their first biological drug, focusing on adverse events and other reasons for discontinuation of the treatment [18]. In the present study, we wanted to extend our analysis to drug survival up to 2 years in the same cohort. We defined the number of patients who achieved at least 50% response and continued the treatment with infliximab, the number of patients who discontinued the treatment and the reason for the discontinuation, and listed the adverse events leading to discontinuation of the treatment.

Patients and methods

In the present study, 104 patients with active RA or SpA were treated with infliximab as their first biological treatment in the Department of Internal Medicine, Center for Rheumatic Diseases of the Tampere University Hospital, Finland. Indication for the commencement of infliximab treatment was based on the national recommendations [17]. The criteria to start infliximab treatment for RA was that the patient suffered from continuously active RA [at least six swollen and tender joints, the duration of morning stiffness of at least 45 min, and/or erythrocyte sedimentation rate (ESR) $\geq$30 mmHg, and/or serum C-reactive protein (CRP) $\geq$28 mg/l] despite treatment with combinations of traditional DMARDs including methotrexate and glucocorticoids [17]. In patients with ankylosing spondylitis (AS), the criteria to start infliximab treatment were: (1) inefficiency of treatment with at least two nonsteroidal anti-inflammatory drugs (NSAIDs) over at least 3 months; (2) sulphasalazine (methotrexate if sulphasalazine contraindicated) or possibly other DMARDs had been ineffective, and (3) the patient had an active disease based on Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ($\geq$4 cm) and on clinical grounds [acute sacroiliitis, elevated acute phase reactants, magnetic resonance imaging (MRI) findings]. In the other spondyloarthropathies, such as psoriatic arthritis (PsA) or inflammatory bowel disease (IBD)-associated arthritis, there were no defined criteria to start treatment with biologicals, but the decision was made on clinical grounds by an experienced rheumatologist based on the severity of arthritis and the inflammatory axial disease, and on criteria available for RA and SpA.

Infliximab was given intravenously at a dose of 3 mg/kg in weeks 0, 2, 6 and every 8 weeks thereafter. The response determined whether the dose was elevated or lowered, or the infusion intervals shortened or lengthened. Infliximab was combined usually with methotrexate and in many cases with other DMARDs (mostly sulphasalazine or hydroxychloroquine) and low-dose prednisolone. The clinical response was carefully followed and registered by an experienced rheumatologist at each visit. In RA, the evaluation included ACR (American College of Rheumatology) response criteria [19] containing the number of swollen and tender joints, the physician's assessment of disease activity (VAS, Visual Analog Scale, 0–10 cm), patient's assessment of general health (VAS), pain (VAS) and HAQ (Health Assessment Questionnaire), and markers of acute phase activity (ESR and CRP). A treatment response lower than ACR50 was regarded as ineffective. In SpA, the clinical response included BASDAI and BASFI (Bath Ankylosing Spondylitis Functional Index), and the treatment was regarded as ineffective if the reduction in BASDAI index was lower than 50% or less than 2 cm.

The drug treatment in addition to infliximab, i.e., glucocorticoids, DMARDs and NSAIDs, was documented. In the case of withdrawal, the reason (adverse event, inefficiency, remission or other reasons) was registered, and cases in which a severe adverse event caused the discontinuation of the treatment were reported to the National Agency of Medicines (NAM).

Results

Patients

In the present study, we analyzed drug survival in patients with active and refractory RA or SpA (n = 104) treated with infliximab as their first biologic drug at the Center for Rheumatic Diseases, Tampere University Hospital during the years 1999–2005. The mean age was 45 years (range 18–75), 64 patients (62%) were female and the mean disease duration was 12 years (range 0.8–52) (Table 1). One or more concomitant DMARDs in addition to infliximab were used in 95% of the patients and 91% were receiving glucocorticoids in accordance with the national recommendations for infliximab treatment (Table 1). A total of 62 (60%) patients had RA, including seropositive disease in 37, seronegative in 15 and juvenile idiopathic arthritis (JIA) in 10 patients (Table 2). A total of 42 (40%) patients had SpA with ankylosing spondylitis in 18, PsA in 8, seronegative oligoarthritis in 5, enteropathic arthritis in 4, reactive arthritis in 4 and sacroiliitis in 3 patients (Table 2).

Table 1 Characteristics of the patients treated with infliximab

	At the beginning	After 2 years infliximab treatment				
	Started	Continued	Discontinued			
	All	All	All	Remission	Inadequate response	Adverse event	Other reason
	(n = 104)	(n = 41)	(n = 62)	(n = 7)	(n = 23)	(n = 25)	(n = 7)
Age, years, mean (range)	45 (18–75)	44 (22–74)	48 (22–76)	44 (22–59)	43 (29–62)	51 (23–75)	55 (24–71)
Females (%)	62	49	71	86	57	76	86
Disease duration, years, mean (range)	12 (0.8–52)	15 (3–31)	13 (1–53)	12 (1–26)	10 (2–23)	15 (2–53)	15 (3–29)
Number of concomitant DMARDs							
0 (%)	5	7	13	0	4	20	28
1 (%)	37	37	35	57	35	32	29
2 (%)	29	19	31	29	26	36	29
3 or more (%)	29	37	21	14	35	12	14
Glucocorticoid intake (%)	91	78	84	71	91	88	100
Glucocorticoid dose (mg/day)	10	4.8	7.8	3.9	10.4	9.1	9.5

One patient was lost during the follow-up (moved to another district)

DMARD disease-modifying antirheumatic drug

Table 2 Infliximab-treated patients according to the diagnosis

Diagnosis	At the beginning	Continuing after 2 years	
	n = 104	n = 41	(40%)
	n	n	%
Rheumatoid arthritis	62	23	37
Seropositive rheumatoid arthritis	37	9	24
Seronegative rheumatoid arthritis	15	8	53
Juvenile idiopathic arthritis	10	6	60
Spondyloarthropathies	42	18	44
Ankylosing spondylitis	18	8	42
Psoriatic arthritis	8	2	25
Seronegative oligoarthritis	5	3	60
Enteropathic arthritis[a]	4	2	50
Reactive arthritis	4	2	50
Sacroiliitis	3	1	33

RA rheumatoid arthritis, *SpA* spondyloarthropathy

[a] Arthritis associated with Crohn's disease or ulcerative colitis

Drug survival in infliximab-treated RA and SpA patients

At the 2 years' time point, 41 (40%) patients had achieved at least a 50% treatment response and the treatment was still ongoing (Table 1). In nine of them, the infliximab treatment was, however, transiently halted during the 2 years' follow-up due to a specific reason (one infection, five remissions, one migraine, one loss of efficacy, and one adverse event from another drug). During 2 years of follow-up, the infliximab treatment had been discontinued in 62 patients (60%) (Table 1). One patient moved to another district and was lost from the follow-up. After 2 years, 23 (37%) RA patients and 18 (44%) SpA patients were still continuing the infliximab treatment (Table 2). In those patients in this group, the number receiving glucocorticoid treatment declined from 93 to 78% and the mean equivalent dose of prednisolone from 10.2 ± 1.1 to 4.7 ± 0.54 mg/day (mean ± SEM $p < 0.0001$) during 2 years of infliximab treatment.

The reasons for discontinuation of infliximab treatment during the 2 years of follow-up are shown in Table 3. During the 2 years' follow-up, 14 patients achieved remission lasting at least 6 months. However, 7 out of the 14 patients re-initiated infliximab treatment during the follow-up due to disease activation, and thus 7 patients were still in remission without infliximab treatment at the 2 years' time point.

The treatment was withdrawn from 23 (22%) patients due to poor efficacy. Six patients discontinued the treatment already during the first 7 months because an adequate

Table 3 Reasons for discontinuing infliximab treatment

Reason	Number	Percent[a]
Remission	7	11
Lack of efficacy	23	37
Adverse event	25	40
Other reasons	7	11
Total	62	100

[a] Percentage of patients who discontinued the medication

response was not attained. Seventeen patients, who initially exhibited an appropriate response were forced to discontinue due to decreasing efficacy.

In 25 (24%) patients, infliximab was discontinued due to an adverse event (Table 4). Of the adverse events, 9 were infections and 14 were hypersensitivity reactions. Two patients discontinued infliximab treatment due to leukopenia. In five patients, infliximab was discontinued for other reasons, i.e., intention to conceive ($n = 2$), technical difficulties in vein cannulation ($n = 2$) and maxillary sinus operation ($n = 1$). Two patients died during the follow-up, one after cerebral infarction and one after myocardial infarction.

Infections

Nine patients with infections were compelled to discontinue infliximab treatment during the 2 years' follow-up. Most of these infections appeared during the first year, and only one thereafter (after 22 months of treatment). Five of the nine infections were pneumonias. One pneumonia patient suffered for several months from fluctuating fever and dyspnea, and she was eventually diagnosed to have mediastinal tuberculosis.

Two cases of septic arthritis appeared during the follow-up, one patient with arthritis in the ankle joint caused by *Staphylococcus aureus* and another with arthritis in the knee caused by *Staphylococcus* species. One patient had a generalized infection with elevated CRP (145 mg/l) with no clinically evident infection focus being detected (Table 4). One 75-year-old female patient suffered from an asymptomatic recurrent urinary tract infection and infliximab treatment was discontinued.

Hypersensitivity reactions

Of the 25 adverse events that required the discontinuation of the infliximab treatment, 14 were hypersensitivity reactions (Table 4), including acute infusion reactions such as urticaria, rash, itching or edema in 11 and delayed hypersensitivity reactions in 3 patients. All hypersensitivity reactions were reduced after discontinuation of the infliximab infusions and glucocorticoid treatment. Three patients did not receive ongoing glucocorticoid treatment at the time of the hypersensitivity reaction.

Other adverse events

Two patients developed leukopenia related to infliximab and the treatment was discontinued. In one 58-year-old patient, with neutrophils 1.4×10^9/l, conventional DMARDs (sulphasalazine and methotrexate) were first discontinued without improvement. Discontinuation of infliximab infusions resulted in a favorable response and leukocyte levels became normalized. Another patient experienced recurrent leukopenia (neutrophils 1.1×10^9/l). Discontinuation of conventional DMARDs had no effect, and leukopenia was only relieved after discontinuation of the infliximab treatment.

Discussion

The treatment of rheumatic diseases with biologicals in Pirkanmaa Health Care District, including the city of Tampere (serving a population of about 500,000), is concentrated at the Center for Rheumatic Diseases, Tampere University Hospital. In the present study, all the patients ($n = 104$) treated with infliximab as their first biological treatment for active RA or SpA according to the national guidelines during 1999–2005 in the Center for Rheumatic Diseases, were analyzed. Infliximab treatment was started for patients with active disease according to the discretion of an experienced rheumatologist, not as a randomized enrollment in a clinical trial. Thus, this analysis of the patient records provided data of the outcomes of infliximab treatment in everyday practice at one rheumatological center.

The main goal in the treatment of active RA is to achieve and maintain remission with a combination of anti-rheumatic drugs [20, 21]. According to the national guidelines, infliximab treatment is added to a combination DMARD therapy when patients have severe and refractory RA despite active treatment with traditional DMARDs. Contrary to the situation in randomized clinical trials, the patients in the present survey had severe and aggressive disease despite ongoing treatment with combinations of two or more DMARDs (not only MTX, which is the case in most randomized clinical trials with TNFα inhibitors). In addition, the doses and numbers of glucocorticoids and NSAIDs were adjusted by the treating rheumatologist.

In the present study, we were able to retrieve patient records during the 2 years' follow-up from all patients who started the treatment with infliximab, except for one subject who moved to another district. A significant loss of patients during follow-up is quite a common phenomenon in many, especially observational, studies [22–24]. Concomitant DMARDs, especially methotrexate, when combined with biological treatment, enhance compliance to the treatment [25] and this may have influenced the very good adherence to the treatment also in the present survey. Combination therapy with methotrexate and infliximab achieved a better response than methotrexate or infliximab as monotherapy [2–4]. As mentioned previously, combination therapy with two or more DMARDs is widely used in Finland [20, 21] and a biological drug is frequently used to supplement combination DMARD therapy. In our previous study, we have

Table 4 Adverse events that led to discontinuation of infliximab treatment

Classification	Nr	Diagnosis	Age (years)	Sex	Disease duration (years)	DMARD's	Time of adverse event (months)	Adverse event
Infection	1	Seronegative oligoarthritis	43	F	19	PRED 5 mg/day MTX 25 mg/week HCQ 257 mg/day	11	Septic arthritis of right knee joint
	2	Seropositive rheumatoid arthritis	49	F	6	MTX 10 mg/week CyA 200 mg/day SSZ 2,000 mg/day	1.5	Pulmonary tuberculosis with mediastinum lymph nodes, diagnosed by biopsy
	3	Seronegative rheumatoid arthritis	51	F	7	PRED 10 mg/day MTX 25 mg/week	5	Infection (CRP 145 mg/ml) with unknown focus
	4	Ankylosing spondylitis	54	M	7	PRED 15 mg/day MTX 25 mg/week SSZ 2,000 mg/day	11	Pneumonia
	5	Ankylosing spondylitis	57	M	15	PRED 7,5 mg/day SSZ 2,000 mg/day HCQ 300 mg/day	22	Pneumonia
	6	Seropositive rheumatoid arthritis	58	F	26	PRED 15 mg/day ATM 50 mg/6week HCQ 300 mg/day	3	Septic arthritis of right ankle joint
	7	Ankylosing spondylitis	50	M	12	SSZ 2,000 mg/day	3	Pneumopericarditis
	8	Seropositive rheumatoid arthritis	71	F	12	PRED 10 mg/day AF 9 mg/day	2	Pneumonia
	9	Seropositive rheumatoid arthritis	75	F	16	PRED 5 mg/day LEF 20 mg/every other day	9	Recurrent urinary tract infections
Hypersensitivity reaction	1	Seropositive rheumatoid arthritis	23	F	2	PRED 5 mg/day	22	Infusion reaction (pain and swelling of throat)
	2	Seronegative rheumatoid arthritis	28	F	15		6	Infusion reaction (rash), DMARDs stopped previously because of mild pharyngitis
	3	Juvenile idiopathic arthritis	31	F	30	PRED 5 mg/day CyA 100 mg/day SSZ 2,000 mg/day AF 3 mg/day	3	Infusion reaction (dyspnoea, rash and itching)
	4	Enteropathic arthropathy	31	M	6	PRED 7,5 mg/day CyA 300 mg/day SSZ 3,000 mg/day	18	Infusion reaction (headache, dyspnoea and rash)

Table 4 continued

Classification	Nr	Diagnosis	Age (years)	Sex	Disease duration (years)	DMARD's	Time of adverse event (months)	Adverse event
	5	Ankylosing spondylitis	35	M	7	MTX 5 mg/week	13	Infusion reaction (dyspnoea, swelling of throat and erythema of face)
	6	Seropositive rheumatoid arthritis	37	F	21	PRED 7,5 mg/day MTX 22,5 mg/week	23	Delayed infusion reaction (itching and rash), developed four days after infusion
	7	Seronegative rheumatoid arthritis	40	M	2	PRED 5 mg/day MTX 10 mg/week SSZ 2,000 mg/day	3	Infusion reaction (rash in upper-body)
	8	Seronegative rheumatoid arthritis	47	F	15	PRED 15 mg/day MTX 20 mg/week SSZ 2,000 mg/day	15	Infusion reaction (rash and itching)
	9	Seropositive rheumatoid arthritis	50	F	7	PRED 10 mg/day AZA 50 mg/day	20	Delayed infusion reaction (rash, itching and edema of face), developed few days after infusion
	10	Seropositive rheumatoid arthritis	52	F	6	CyA 150 mg/day SSZ 3,000 mg/day HCQ 214 mg/day	5	Infusion reaction (dyspnea, rash and cough)
	11	Seropositive rheumatoid arthritis	54	F	11	PRED 10 mg/day MTX 20 mg/week	1.5	Infusion reaction (malaise, chills and rash)
	12	Seropositive rheumatoid arthritis	73	F	25	MTX 5 mg/week	15.5	Infusion reaction (rash and itching in the hand)
	13	Psoriatic arthropathy	73	F	15	PRED 10 mg/day	5.5	Delayed infusion reaction (rash, dyspnea), developed two days after infusion
	14	Seropositive rheumatoid arthritis	75	F	53	PRED 5 mg/day CyA 100 mg/day SSZ 2,000 mg/day	6	Infusion reaction (hoarseness, dyspnea, rash)
Other reasons	1	Seropositive rheumatoid arthritis	44	F	15	PRED 10 mg/day CyA 150 mg/day HCQ 214 mg/day	24	Recurrent cytopenia/neutropenia (0.85–l.1 × 10 9/l)
	2	Enteropathic arthropathy	58	F	22	PRED 5 mg/day SSZ 1,000 mg/day	5	Cytopenia/neutropenia (1.4 × 10 9/l)

DMARD disease-modifying antirheumatic drug, *AF* auranofin, *ATM* aurothiomalate, *AZA* azathioprine, *CyA* cyclosporin A, *HCQ* hydroxychloroquine, *MTX* methotrexate, *PRED* prednisolone, *SSZ* sulfasalazine

shown that in patients with refractory RA or SpA, the addition of etanercept or adalimumab to a combination of traditional DMARDs resulted in good, as well as a favorable treatment response, during 12 months' follow-up [26].

In the initial clinical randomized studies, Maini et al. [1] reported continuation rates up to 91% with ACR20 criteria after 30 weeks of infliximab treatment depending on the dose and infusion intervals. In the study of Lipsky et al. [2], a continuation rate of 79% was reported after 54 weeks of treatment. In observational studies, continuation rates are usually lower than in clinical randomized trials; 66% of the patients continued infliximab infusions after 1 year [8], and after 2 years' intervention 67% [9] and 73% [10] drug survival rates were reported. In the study of Buch et al. [14] only 27 out of 174 patients (16%) continued infliximab treatment at the 24 months' time point. In the present study, 40% of the patients continued with infliximab treatment after the 2 years' follow-up since they had achieved at least a 50% response without any severe adverse event or other reason requiring discontinuation of the treatment. In addition, 7 (7%) of 104 patients had discontinued infliximab treatment due to remission.

In the present study, the continuation rate was 35% in RA patients and 44% in SpA patients. Although the difference was small, it confirms the results obtained in previous studies. In a Spanish study, SpA patients had a 33% lower probability to discontinue the biologicals than RA patients [27]. Recently, Heiberg et al. [28] reported a higher continuation rate among patients with AS or PsA versus RA patients. In some clinical trials, infliximab has been given at higher doses and/or shorter intervals to patients with SpA than in patients with RA [6, 7]. In the present study, infliximab treatment was started at a dose of 3 mg/kg also in SpA patients and, if needed, the dose was increased and/or the infusion interval was adjusted in conjunction with the response. Accordingly, Braun et al. [7] concluded in their review that often a dose of 3 mg/kg is adequate also in SpA patients. However, there are data showing that increasing the infliximab dose in SpA patients after 36 weeks of treatment from 5 to 7.5 mg/kg achieved no better efficacy [6].

The response to infliximab treatment is evident already after 2 weeks of treatment, when over 50% of the RA patients have been reported to achieve ACR20 response [1]. There is probably some variation in the onset time of the response, and the effect of the drug treatment can also wane with time. It was recently reported that in RA an increase in frequency of infusions may contribute to a more constant effect than an increase in the dose [29]. In the study of Figueiredo et al. [16], nearly 40% of the RA patients required an increase of the dose or a shortening of the interval between the infliximab infusions or both to maintain relief of symptoms. In the present study, the average discontinuation time among the 23 patients with an inadequate response was 11 months after treatment initiation. According to the patients' records, 6/23 patients discontinued the treatment due to inadequate response during the first 7 months, and 17/23 patients had an appropriate response at the beginning, but discontinued the treatment later because of waning efficacy. Buch et al. [14] reported also that some patients could not maintain an already achieved response at later time points. In observational studies, the rate of discontinuation due to inefficacy varies between 9.2 and 11% [8, 10, 16]. In clinical studies, discontinuation rates due to inefficacy are around 10% [1, 2]. It is worth noticing that the continuation criteria in those studies have been mostly set as ACR20 and not ACR50 as in the present study, which is the clinical practice in Finland.

The formation of antibodies against infliximab has been reported in clinical trials [1, 3], and anti-infliximab antibodies are more often found in patients with reduced response [30]. In addition, there is also evidence of the association between antibody formation and increased infliximab clearance [31]. In the present study, antibodies against infliximab were not measured. It is possible that the dissipating efficacy was due to decreased concentrations of active infliximab as a result of the formation of infliximab–antibody complex or to differences in the metabolism of infliximab in individual patients [32].

In the present study, only those adverse events that led to discontinuation of infliximab treatment were registered. Those were serious and often required either medical treatment or hospitalization. During the 2 years' follow-up, 24% of all patients were compelled to discontinue the medication due to adverse events. Infection was responsible for discontinuation of the treatment in 9% of the patients. In RA, there is an increased risk for infections [33, 34]. Traditional DMARDs have been reported to further elevate the risk [35–37], but there are also contradictory findings [38]. Biologicals have also a tendency to increase the risk of infections [11, 39, 40] in RA patients. We observed in the present study a higher number of infections, which caused discontinuation of treatment during the first year of treatment than in the second year. These data are in agreement with the results of Curtis et al. who reported a fourfold greater risk of infections during the first 6 months of infliximab treatment [39]. The most frequently occurring severe infections during infliximab treatment are pulmonary, skin, soft tissue, joint and bone infections, and also septic infections are slightly more probable in RA patients treated with biological agents than in those treated with conventional DMARDs [11–13, 40]. Oral glucocorticoids have also been reported to elevate the risk of infections in patients with RA even at a dose less than 5 mg/day [35, 37, 38]. In active and severe RA or SpA, the use of biologicals in addition to combinations of DMARDs and oral glucocorticoidsis is probably associated with a high risk for infections and this

should be taken into account clinically and when interpreting the results of the present study.

Hypersensitivity reactions appear to be related to infliximab infusions quite often, but these are usually benign. In previous reports, hypersensitivity reactions have been a notable reason for discontinuation of infliximab treatment, and they have most frequently occurred during the second to fourth infusion [14, 15] manifesting as urticaria, rash, itching and dyspnea. In the clinical study of Maini et al. [1], hypersensitivity reactions appeared most commonly during the first infusion. In our study, 13% of the patients had to discontinue infliximab treatment due to a hypersensitivity reaction and half of these reactions occurred during the first 6 months. In the present study, three patients with a hypersensitivity reaction did not receive glucocorticoid treatment in addition to the infliximab and DMARDs. Augustsson et al. [41] reported that daily low-dose glucocorticoids lowered the risk of treatment-limiting infusion reactions to infliximab.

In previous studies, only a few cases of leukopenias have been reported [9, 42–44]. In the present study, two patients developed leukopenia during the 2 years of follow-up. In a recent analysis of 1,440 patients with rheumatic disease who were treated with a biological drug, four patients with leukopenias were reported [45].

In the present study, RA and SpA patients with active disease despite ongoing treatment with combinations of DMARDs were treated with infliximab as their first biological drug. Drug survival after 2 years of follow-up was 40%, when ACR50 (or 50% reduction in BASDAI) was set as the response criteria. As compared to our previous results with 6 months' follow-up [18], drug survival decreased, mainly due to waning efficacy and an increasing number of adverse events. Infections and hypersensitivity reactions were the most common adverse events, which were responsible for the discontinuation of treatment. In addition, two patients with drug-related leukopenia were diagnosed.

Acknowledgments We thank Mrs. Heli Määttä and Mrs. Heli Pikkuharju for their excellent secretarial help. The study was supported by the Clinical Drug Research Graduate School, Finland and the Competitive Research Funding of the Pirkanmaa Hospital District.

References

1. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M, 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 354:1932–1939
2. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, Smolen JS, Weisman M, Emery P, Feldmann M, Harriman GR, Maini RN, Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group (2000) Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 343:1594–1602
3. 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, Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group (2004) Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 50:3432–3443
4. 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, 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 52:3381–3390
5. van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, Braun J, Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group (2005) Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 52:582–591
6. Braun J, Deodhar A, Dijkmans B, Geusens P, Sieper J, Williamson P, Xu W, Visvanathan S, Baker D, Goldstein N, van der Heijde D, Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group (2008) Efficacy and safety of infliximab in patients with ankylosing spondylitis over a two-year period. Arthritis Rheum 59:1270–1278
7. Braun J, Baraliakos X, Brandt J, Sieper J (2005) Therapy of ankylosing spondylitis. Part II. Biological therapies in the spondyloarthritides. Scand J Rheumatol 34:178–190
8. Flendrie M, Creemers MC, Welsing PM, den Broeder AA, van Riel PL (2003) Survival during treatment with tumour necrosis factor blocking agents in rheumatoid arthritis. Ann Rheum Dis 62(Suppl 2):ii30–ii33
9. Wendling D, Materne GE, Michel F, Lohse A, Lehuede G, Toussirot E, Massol J, Woronoff-Lemsi MC (2005) Infliximab continuation rates in patients with rheumatoid arthritis in everyday practice. Joint Bone Spine 72:309–312
10. Voulgari PV, Alamanos Y, Nikas SN, Bougias DV, Temekonidis TI, Drosos AA (2005) Infliximab therapy in established rheumatoid arthritis: an observational study. Am J Med 118:515–520
11. Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, Gromnica-Ihle E, Antoni C, Herzer P, Kekow J, Schneider M, Zink A (2005) Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum 52:3403–3412
12. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP, British Society for Rheumatology Biologics Register (2006) Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 54:2368–2376
13. Salliot C, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S, Dougados M (2007) Infections during tumour necrosis factor-{alpha} blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology (Oxford) 46:327–334
14. Buch MH, Bingham SJ, Bryer D, Emery P (2007) Long-term infliximab treatment in rheumatoid arthritis: subsequent outcome of initial responders. Rheumatology (Oxford) 46:1153–1156

15. Wasserman MJ, Weber DA, Guthrie JA, Bykerk VP, Lee P, Keystone EC (2004) Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. J Rheumatol 31:1912–1917
16. Figueiredo IT, Morel J, Sany J, Combe B (2008) Maintenance and tolerability of infliximab in a cohort of 152 patients with rheumatoid arthritis. Clin Exp Rheumatol 26:18–23
17. Working group set up by Finnish Medical Society Duodecim and Finnish Society for Rheumatology, Helsinki, Finland. (Updated 18 Sep 2009) Rheumatoid arthritis Current Care Guideline. Finnish Medical Society Duodecim. http://www.kaypahoito.fi (in Finnish). Accessed at 06 Oct 2009
18. Levälampi T, Korpela M, Vuolteenaho K, Moilanen E (2008) Infliximab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: adverse events and other reasons for discontinuation of treatment. Scand J Rheumatol 37:6–12
19. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, Katz LM, Lightfoot R Jr, Paulus H, Strand V (1995) American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 38:727–735
20. 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, Jarvinen P, Hakola M, Piirainen H, Ahonen J, Palvimaki I, Forsberg S, Koota K, Friman C (1999) Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 353:1568–1573
21. Mäkinen H, Kautiainen H, Hannonen P, Möttönen T, Leirisalo-Repo M, Laasonen L, Korpela M, Blåfield H, Hakola M, Sokka T (2007) Sustained remission and reduced radiographic progression with combination disease-modifying antirheumatic drugs in early rheumatoid arthritis. J Rheumatol 34:316–321
22. Feltelius N, Fored CM, Blomqvist P, Bertilsson L, Geborek P, Jacobsson LT, Lindblad S, Lysholm J, Rantapaa-Dahlqvist S, Saxne T, Klareskog L, ARTIS Group (2005) Results from a nationwide postmarketing cohort study of patients in Sweden treated with etanercept. Ann Rheum Dis 64:246–252
23. Brocq O, Roux CH, Albert C, Breuil V, Aknouche N, Ruitord S, Mousnier A, Euller-Ziegler L (2007) TNFalpha antagonist continuation rates in 442 patients with inflammatory joint disease. Joint Bone Spine 74:148–154
24. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, Falappone PC, Ferrante A, Malesci D, Massara A, Nacci F, Secchi ME, Manganelli S, Salaffi F, Bambara ML, Bombardieri S, Cutolo M, Ferri C, Galeazzi M, Gerli R, Giacomelli R, Grassi W, Lapadula G, Cerinic MM, Montecucco C, Trotta F, Triolo G, Valentini G, Valesini G, Ferraccioli GF, GISEA group (2007) Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. J Rheumatol 34:1670–1673
25. Kristensen LE, Saxne T, Nilsson JA, Geborek P (2006) Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther 8:R174
26. Levälampi T, Korpela M, Vuolteenaho K, Moilanen E (2008) Etanercept and adalimumab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: adverse events and other reasons leading to discontinuation of the treatment. Rheumatol Int 28:261–269
27. Carmona L, Gomez-Reino JJ, BIOBADASER Group (2006) Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis. Data from the Spanish registry BIOBADASER. Arthritis Res Ther 8:R72
28. Heiberg MS, Koldingsnes W, Mikkelsen K, Rodevand E, Kaufmann C, Mowinckel P, Kvien TK (2008) The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum 59:234–240
29. van Vollenhoven RF, Klareskog L (2007) Infliximab dosage and infusion frequency in clinical practice: experiences in the Stockholm Biologics Registry STURE. Scand J Rheumatol 36:418–423
30. Wolbink GJ, Vis M, Lems W, Voskuyl AE, de Groot E, Nurmohamed MT, Stapel S, Tak PP, Aarden L, Dijkmans B (2006) Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis Rheum 54:711–715
31. Xu Z, Seitz K, Fasanmade A, Ford J, Williamson P, Xu W, Davis HM, Zhou H (2008) Population pharmacokinetics of infliximab in patients with ankylosing spondylitis. J Clin Pharmacol 48:681–695
32. St Clair EW, Wagner CL, Fasanmade AA, Wang B, Schaible T, Kavanaugh A, Keystone EC (2002) The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 46:1451–1459
33. Mutru O, Laakso M, Isomäki H, Koota K (1985) Ten-year mortality and causes of death in patients with rheumatoid arthritis. Br Med J (Clin Res Ed) 290:1797–1799
34. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE (2002) Predictors of infection in rheumatoid arthritis. Arthritis Rheum 46:2294–2300
35. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA, Chan KA (2008) The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol 35:387–393
36. Caporali R, Caprioli M, Bobbio-Pallavicini F, Montecucco C (2008) DMARDS and infections in rheumatoid arthritis. Autoimmun Rev 8:139–143
37. Bernatsky S, Hudson M, Suissa S (2007) Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford) 46:1157–1160
38. Lacaille D, Guh DP, Abrahamowicz M, Anis AH, Esdaile JM (2008) Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis Rheum 59:1074–1081
39. Curtis JR, Patkar N, Xie A, Martin C, Allison JJ, Saag M, Shatin D, Saag KG (2007) Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 56:1125–1133
40. Favalli EG, Desiati F, Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB, Gorla R, Filippini M, Marchesoni A (2009) Serious infections during anti-TNFalpha treatment in rheumatoid arthritis patients. Autoimmun Rev 8:266–273
41. Augustsson J, Eksborg S, Ernestam S, Gullstrom E, van Vollenhoven R (2007) Low-dose glucocorticoid therapy decreases risk for treatment-limiting infusion reaction to infliximab in patients with rheumatoid arthritis. Ann Rheum Dis 66:1462–1466
42. Vidal F, Fontova R, Richart C (2003) Severe neutropenia and thrombocytopenia associated with infliximab. Ann Intern Med 139:W–W63
43. Favalli EG, Varenna M, Sinigaglia L (2005) Drug-induced agranulocytosis during treatment with infliximab in enteropathic spondyloarthropathy. Clin Exp Rheumatol 23:247–250
44. Montane E, Salles M, Barriocanal A, Riera E, Costa J, Tena X (2007) Antitumor necrosis factor-induced neutropenia: a case

report with double-positive rechallenges. Clin Rheumatol 26:1527–1529
45. Konttinen L, Honkanen V, Uotila T, Pöllänen J, Waahtera M, Romu M, Puolakka K, Vasala M, Karjalainen A, Luukkainen R, Nordström DC, for the ROB-FIN study group (2006) Biological treatment in rheumatic diseases: results from a longitudinal surveillance: adverse events. Rheumatol Int 26:916–922