Tampere University

PAULA MUILU

Inflammatory Arthritides in Finland

Incidence, Early Treatment and Opioid Use

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ACADEMIC DISSERTATION
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ACADEMIC DISSERTATION
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PunaMusta Oy – Yliopistopaino
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To my family

ABSTRACT

The treatment of inflammatory arthritis (IA) often requires permanent patient monitoring at rheumatology clinics, leading to an increased burden on specialist care and elevated health care costs. Epidemiological incidence studies are important in the planning of health care resources. In recent decades, the pharmacotherapy for IAs has intensified with the introduction of new disease-modifying anti-rheumatic drugs (DMARDs) to the market. The current treatment recommendations for early IA aim at active DMARD initiation and rapid disease remission. Despite the intensification of drug therapy, IA patients' pain management remains a challenge. Increasing opioid use is causing worldwide concern, and there is insufficient evidence for the benefits of opioids in the management of arthritis pain.

The objectives of this study were to investigate the trends in the incidences of IAs in Finland during this millennium, and to obtain data on IA patients' early DMARD therapies and the implementation of treatment recommendations, as well as the patients' analgetic use, with a special emphasis on opioids. The data were collected from the registries maintained by the Finnish Social Insurance Institution, and patients were compared with general population controls matched for age, gender, and place of residence by the Population Register Centre. In terms of incidence, a wider range of IAs was observed, whereas the other three substudies focused on rheumatoid arthritis (RA), undifferentiated arthritis (UA), and axial spondyloarthritis (axSpA).

It turned out that between 2000 and 2014, the age-standardized total incidence of IAs in Finland was 115 for women and 70/100,000 for men. Between the five-year cohorts 2000-2004 and 2010-2014, the incidence of axSpA, UA, and psoriatic arthritis increased significantly. No significant change was observed in the incidence of seropositive RA, whereas the incidence of seronegative RA declined. The mean age at diagnosis of an IA decreased in women from 53 to 51 years.

The treatment of early RA and UA was initiated actively in Finland. At one month from diagnosis, more than 90% of RA patients and nearly as many UA patients had started a conventional synthetic (cs) DMARD, most commonly methotrexate (MTX). The triple combination of csDMARDs recommended in the Current Care Guidelines was initiated by 22% of seropositive RA patients. The use of self-injected

biological (b) DMARDs was low during the first year of follow-up. Treatment of axSpA was started with a csDMARD, most commonly sulfasalazine or MTX, and less than 14% of the patients started a self-injected bDMARD within a year of diagnosis.

Individual opioid purchases as well as long-term opioid use were more common among IA patients compared to the population controls, and this difference was 5-14% depending on the IA diagnosis. The risk ratio of opioid purchases among IA patients compared to the controls was greatest in the three-month period prior to diagnosis, and it decreased after the assumed DMARD initiation during the one-year follow-up, especially among seropositive RA patients. Although the axSpA patients' mean age at diagnosis was lower than in the other studied IA groups, a larger proportion of them (30% a year before and 22% a year after the diagnosis) used opioids compared to RA and UA patients. Among Finnish IA patients, the opioid use concentrated on mild opioids and was relatively less common than in most other Western countries. AxSpA patients' opioid consumption (in defined daily doses) decreased during the 12-months of follow-up among those to whom bDMARDs were started between 2010 and 2015.

In conclusion, during the 15-year observation period, the total incidence of IAs increased somewhat. The treatment of RA was initiated early and often with MTX-based combination therapy. In the early treatment of axSpA, the proportions of users of self-injected bDMARDs were quite low, but the initiation of a bDMARD appeared to reduce these patients' opioid consumption. The risk for opioid use was higher among IA patients compared to their population controls. Taken together, the population's increasing life expectancy and the fact that IA patients' treatment often requires long-term monitoring in rheumatology clinics, the burden caused by IAs on the health care system and especially on specialist care will probably increase in the future.

TIIVISTELMÄ

Tulehduksellisten reumasairauksien hoito edellyttää yleensä pitkäaikaista seurantaa reumaklinikoissa kuormittaen erikoissairaanhoitoa ja aiheuttaen kustannuksia. Epidemiologiset tutkimukset tautien ilmaantuvuudesta ovat tärkeitä terveydenhuollon resurssien suunnittelussa. Viime vuosikymmenten aikana tulehduksellisten reumasairauksien lääkehoito on tehostunut uusien lääkkeiden tultua markkinoille. Nykyiset varhaisen tulehduksellisen reumasairauden hoitosuositukset tähtäävät hoidon aktiiviseen aloitukseen ja taudin nopeaan remissioon. Lääkehoidon tehostumisesta huolimatta reumapotilaiden kivun hoito on edelleen haastavaa. Opioidien käytön lisääntyminen aiheuttaa huolta maailmanlaajuisesti, eikä reumasairauksien osalta ole juurikaan näyttöä opioidien hyödyistä kivun hoidossa.

Tämän tutkimuksen tavoitteina oli luoda käsitys tulehduksellisten reumasairauksien ilmaantuvuuksista tällä vuosituhannella, alkuvaiheen lääkityksistä ja hoitosuositusten toteutumisista sekä potilaiden kipulääkityksistä erityisesti opioidien osalta. Aineistona toimivat Suomen Kansaneläkelaitoksen kattavat rekisteritiedot ja väestörekisterikeskuksen potilaille kaltaistamat ikä-, sukupuoli- ja asuinpaikkavakioidut verrokit. Ilmaantuvuuden osalta tarkasteltiin laajempaa tulehduksellisten reumasairauksien joukkoa, mutta kolmessa muussa osatyössä keskityttiin nivelreumaan, luokittelemattomaan niveltulehdukseen eli artriittiin sekä aksiaaliseen spondyloartriittiin.

Osoittautui, että vuosina 2000-14 tulehduksellisten reumasairauksien ikävakioitu kokonaisilmaantuvuus Suomessa oli naisilla keskimäärin 115 ja miehillä 70/100 000 henkilövuotta. Viisivuotiskohorttien 2000-04 ja 2010-14 välillä aksiaalisen spondyloartriitin, luokittelemattoman artriitin sekä nivelpsoriaasin ilmaantuvuus suureni merkitsevästi. Seropositiivisen nivelreuman ilmaantuvuudessa ei havaittu merkitsevää muutosta, sen sijaan seronegatiivisen nivelreuman ilmaantuvuus pieneni. Keskimääräinen ikä reumasairauden diagnoosivaiheessa laski naispotilailla 53 vuodesta 51 vuoteen.

Tuoreen nivelreuman ja luokittelemattoman artriitin hoito aloitettiin Suomessa aktiivisesti. Kuukauden kohdalla diagnoosista yli 90 % nivelreumapotilaista ja lähes yhtä moni luokittelematonta artriittia sairastavista potilaista oli aloittanut perinteisen

reumalääkkeen, yleisimmin metotreksaatin. Käypä hoito -suositusten mukaisen kolmen antireumaatin (REKO) yhdistelmän aloitti 22 % seropositiivista nivelreumaa sairastavista taudin alkuvaiheessa. Itsepistettävien biologisten reumalääkkeiden käyttö oli vähäistä ensimmäisen seurantavuoden aikana. Aksiaalisen spondyloartriitin hoito aloitettiin perinteisellä reumalääkkeellä, yleisimmin sulfasalatsiinilla tai metotreksaatilla ja vajaa 14 % potilaista aloitti itsepistettävän biologisen lääkkeen vuoden sisällä diagnoosista.

Yksittäiset opioidiostot ja opioidien pitkäaikaiskäyttö olivat yleisempiä tulehduksellista reumatautia sairastavilla potilailla verrattuna väestökontrolleihin ja tämä erotus oli 5-14% riippuen diagnoosista. Potilaiden opioidiostojen suhteellinen riski kontrolleihin verrattuna oli suurimmillaan 3 kuukauden ajanjaksolla ennen diagnoosia ja väheni reumalääkityksen aloituksen jälkeen vuoden seurannassa erityisesti seropositiivista nivelreumaa sairastavilla. Vaikka aksiaalisista spondyloartriittia sairastavien potilaiden diagnoosihetken keski-ikä oli muita tutkittuja diagnoosiryhmiä alhaisempi, heistä suurempi osa käytti opioideja nivelreumaa tai luokittelematonta artriittia sairastaviin potilaihin verrattuna. Suomalaisilla reumatautipotilailla opioidien käyttö keskittyi mietoihin opioideihin ja käyttäneitä oli suhteessa vähemmän kuin useimmissa muissa länsimaissa. Aksiaalista spondyloartriittia sairastavilla potilailla opioidien kulutus (määriteltyinä vuorokausiannoksina) väheni 12 kuukauden seurannassa niillä potilailla, joille oli aloitettu biologinen reumalääke vuosina 2010-15.

Yhteenvetona todetaan, että 15 vuoden tarkastelujaksolla tulehduksellisten reumasairauksien ilmaantuvuus kokonaisuutena suureni jonkin verran. Nivelreuman hoito aloitettiin varhain ja usein metotreksaattia sisältävällä yhdistelmähoidolla. Aksiaalisen spondyloartriitin varhaishoidossa itsepistettäviä biologisia lääkkeitä käyttäneiden osuus oli pienehkö, mutta heillä biologinen lääke näytti vähentäneen opioidien kulutusta seurannassa. Riski käyttää opioideja oli tulehduksellisiin reumatauteihin sairastuneilla suurempi kuin heidän väestöverrokeillaan. Huomioiden sekä väestön pitenevä elinikä että tulehduksellisten reumasairauksien monesti vuosia jatkuva hoito reumaklinikoissa, kuormittavat ne todennäköisesti etenevästi terveydenhuoltoa ja erityisesti erikoissairaanhoitoa tulevaisuudessa.

CONTENTS

ABREVIATIONS

ACPA	anti-citrullinated peptide antibody
ACR	American College of Rheumatology
AS	ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ATC	Anatomical Therapeutic Chemical
AxSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
bDMARD	biological disease-modifying anti-rheumatic drug
CASPAR	Classification Criteria for Psoriatic Arthritis
CDAI	Clinical Disease Activity Index
CI	confidence interval
COX	cyclo-oxygenase
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying anti-rheumatic drug
DAS-28	Disease Activity Score assessing 28 joints
DDD	defined daily dose
DMARD	disease-modifying anti-rheumatic drug
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GC	glucocorticoid
GI	gastrointestinal
HCQ	hydroxychloroquine
HLA	human leukocyte antigen
IA	inflammatory arthritis
IBD	inflammatory bowel disease
ID	index date
IFX	infliximab
IL	interleukin

IL-17i	interleukin-17 inhibitor
IRR	incidence rate ratio
IQR	interquartile range
JAK	Janus kinase inhibitor
LEF	leflunomide
MRI	magnetic resonance imaging
MTX	methotrexate
Nr-axSpA	non-radiographic axial spondyloarthritis
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PGA	patient global assessment
PMR	polymyalgia rheumatica
PRD	prednisolone or prednisone
PsA	psoriatic arthritis
QALY	quality-acquired life years
RA	rheumatoid arthritis
ReA	reactive arthritis
RF	rheumatoid factor
RR	risk ratio
RTX	rituximab
SDAI	simplified disease activity index
SE	shared epitope
SII	Social Insurance Institution
SLE	systemic lupus erythematosus
SpA	spondyloarthritis
SR	special reimbursement
SS	Sjögren's syndrome
SSZ	sulfasalazine
SD	standard deviation
tDMARD	targeted disease modifying anti-rheumatic drug
TNF	tumour necrosis factor
TNFi	tumour necrosis factor inhibitor
T2T	treat-to-target
UA	undifferentiated arthritis
UCTD	undifferentiated connective tissue disorder
VAS	visual analogue scale

ORIGINAL PUBLICATIONS

I Muilu P, Rantalaiho V, Kautiainen H, Virta LJ, Eriksson JG, Puolakka K. Increasing incidence and shifting profile of idiopathic inflammatory rheumatic diseases in adults during this millennium. Clin Rheumatol 2019;38:555-62.

II Muilu P, Rantalaiho V, Kautiainen H, Virta LJ, Eriksson JG, Puolakka K. First-year drug therapy of new-onset rheumatoid and undifferentiated arthritis: A nationwide register-based study. BMC Rheumatol 2020;4:34.

III Muilu P, Rantalaiho V, Kautiainen H, Virta LJ, Puolakka K. Opioid use among patients with early inflammatory arthritides compared to the general population. J Rheumatol 2020;47:1285-92.

IV Muilu P, Rantalaiho V, Kautiainen H, Virta LJ, Puolakka K. Opioid use frequency in early axial spondyloarthritis in Finland: A pharmacoepidemic register study. Submitted for publication.

1 INTRODUCTION

Idiopathic inflammatory arthritis (IA) is a group of autoimmune disorders characterized by inflammation of the joints and other tissues, such as tendons or the spine. Until the early 1990s, different IAs commonly caused joint or spine destruction, disability, incapacity to work, and increased mortality; however, better drug treatment possibilities have made these diseases manageable. Today, the treatment of IAs is mainly outpatient-based and the need for rheumatology wards in hospitals has dropped. However, there is no cure for IAs; they are chronic diseases that often require life-long treatments and monitoring at rheumatology clinics.

Epidemiological studies investigating the trends in the incidence of IAs are important in many ways: they can help to better know the factors that have an impact on the initiation of IA, allow comparison of incidence rates between different subgroups, and also help to plan appropriately patients' and the community's future health care needs and estimate the burden caused by IAs, since both the costly treatments as well as the outcomes (e.g. inability to work, need for joint replacement surgeries or hospital stays) of IAs have vast economic consequences for societies.

However, comparing epidemiological studies from different countries is challenging because of differing methods. In addition, the concept of various IAs and consequently classification criteria have changed over time. Case identification is the key issue. Examining the whole population is the gold standard, but it is rarely possible. Thus, almost all studies are based on hospital or insurance data not primarily intended for epidemiological research. Most early arthritis studies are based on samples of the population (Savolainen et al. 2003, Kononoff et al. 2017, Söderlin et al. 2002, Yu et al. 2013). National registers are found in some countries.

Contemporary recommendations of drug therapy for IAs emphasize the importance of early treatment aiming at clinical remission to reduce or prevent consequent damage caused by continuous inflammation. In rheumatoid arthritis (RA), the key role of methotrexate (MTX) has broadly been accepted, but the role of the initial use of combinations of conventional synthetic disease-modifying anti-

rheumatic drugs (csDMARDs) causes disagreement (Singh et al. 2016, Smolen et al. 2017). The latest Finnish National Guideline from 2015 supports the initiation of three csDMARDs, the so-called FIN-RACo combination and low-dose glucocorticoid (GC) in early, active RA (Current Care Guideline 2015). Also, in undifferentiated arthritis in which no specific classification criteria are fulfilled, the early and active treatment strategy is recommended to prevent further joint damage and disability, and the first drug of choice should preferably be MTX (Combe et al. 2017). In active axSpA, the international treatment guidelines recommend the initiation of biological DMARDs (bDMARDs) after the failure of non-steroidal anti-inflammatory drugs (NSAIDs)(Ward et al. 2016, Ward et al. 2019, van der Heijde et al. 2017). In Finland, however, a try-out with at least one csDMARD is required to be granted a special reimbursement before proceeding to bDMARDs (Social Insurance Institution Drug Requirements). Regardless of the various drug treatment guidelines encouraging early active treatment, adherence to these guidelines in practice by both the physicians and the patients may vary substantially.

Although the drug therapies have advanced, IA patients' pain management remains a challenge. Both inflammatory and mechanical factors, as well as central sensitization contribute to the onset of pain. In recent years, the liberal management of chronic noncancer pain with opioids has partially contributed to the current worldwide opioid epidemic. However, studies investigating the effectiveness of opioids in arthritis or muscle and joint pain usually emphasize the risks of adverse effects and do not support the benefits of long-term opioid treatment or the use of strong opioids; further, the follow-up periods of these studies are often short in duration (Whittle et al. 2011, Whittle et al. 2012a, Whittle et al. 2013, Chaparro et al. 2014, Hayes et al. 2018). Current recommendations therefore state that opioids should only be used in carefully considered cases for IA (Whittle et al. 2012a, Whittle et al. 2013).

The studies in this thesis, which use national register data, were planned with the aim of gaining novel information on the temporal trends of IA incidences, the implementation of drug treatment in early IA, and the pain medications used by IA patients with a special emphasis on opioids.

2 REVIEW OF THE LITERATURE

2.1 Definition of inflammatory arthritis (IA)

Idiopathic inflammatory arthritis (IA) is a group of autoimmune disorders including rheumatoid arthritis (RA), axial spondyloarthritis [axSpA, including ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)], psoriatic arthritis (PsA), juvenile arthritis, reactive arthritis (ReA), arthritis associated with inflammatory bowel disease (IBD), systemic connective tissue disorders [systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), etc.], and undifferentiated arthritis (UA). In autoimmune disorders, the immune system mistakenly attacks itself, causing a failure of immunological tolerance, which normally prevents the inflammatory cells from recognizing self-antigens (Wahren-Herlenius and Dörner 2013). IAs are characterized by the inflammation of joints and other tissues, such as tendons and the spine.

2.1.1 Rheumatoid arthritis (RA)

RA is a chronic and progressive autoimmune disorder characterized by systemic inflammation mainly presenting in the synovial joints. RA usually attacks symmetrically the small- and medium-sized joints of the body, and the inflammation eventually leads to joint destruction if left untreated. Numerous extra-articular manifestations, such as rheumatoid nodules, pulmonary involvement, or vasculitis, may be present (Smolen et al. 2016a). Also, different comorbidities, such as cardiovascular disease, diabetes, interstitial lung disease, malignancies, gastro-intestinal disorder, osteoporosis, and depression are associated with RA (Agca et al. 2016, Jiang et al. 2015, Bongatz et al. 2010, Raheel et al. 2016, Myasoedova et al. 2011, Choi et al. 2018, Matcham et al. 2013).

RA can be divided into two subtypes by serological phenotype: rheumatoid factor (RF) and anti-citrullinated peptide (ACPA) negative, and RF and/or ACPA positive.

These serotypes are nowadays recognized as two aetiologically distinct subtypes with different risk factor associations (Pedersen et al. 2006).

There are no actual diagnostic criteria for RA, but the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for RA published in 2010 (Table 1) are often used as a diagnostic tool. The patient must have at least one joint with definite swelling that is not explained by another disease. These new criteria score the disease according to the number and location of swollen joints, inflammation markers, and serology, and they are better at identifying early RA than the previous ACR 1987 classification criteria (Aletaha et al. 2010). The scoring system emphasizes a positive serology. Consequently, seronegative oligoarthritis can no longer be classified as rheumatoid arthritis, as was the case before 2010. According to the latest criteria, a score of ≥6 is indicative of the presence of definite RA, whereas a score between 3 and 5 indicates possible RA. Also, patients with typical erosive radiographic findings may be diagnosed as having RA, although they do not fulfil these classification criteria.

Table 1. The 2010 ACR/EULAR classification criteria for RA (modified from Aletaha et al. 2010).

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

2.1.2 Undifferentiated arthritis (UA)

UA does not fit into any particular IA diagnostic category, so it is frequently used as a working diagnosis for patients with early IA after specific forms of arthritis are excluded. Later on, UA may develop into a more specific established disease, resolve spontaneously, or remain unspecified (Combe et al. 2017). Some countries, excluding Finland, have specific early arthritis clinics.

2.1.3 Axial spondyloarthritis (axSpA)

AxSpA (including nr-axSpA and AS) belongs to a broader group called spondyloarthritis (SpA). Peripheral phenotypes of SpA include psoriatic arthritis (PsA), reactive arthritis (ReA), IBD-associated arthritis, and undifferentiated peripheral SpA (Figure 1). However, the clinical presentation may overlap between the groups. In axSpA, the inflammation of the sacroiliac joints and the spine is usually present at diagnosis, but the disease can also appear predominantly as peripheral joint arthritis (Bohn 2018). Typical disease manifestations include enthesitis, dactylitis, uveitis, and colitis. Also, cardiac involvement, such as aortic insufficiency, aortitis, or conduction abnormalities, may be present (Ozkan 2016). AxSpA usually starts with symptoms like back and buttock pain. The reported gender ratios (males:females) range between 1.2-7.0:1 (Dean et al. 2014).

Familial aggregation may be present since axSpA is associated with human leucocyte antigen (HLA)-B27; however, only some individuals carrying HLA-B27 develop axSpA. In AS, definite radiographic sacroiliitis is visible in plain x-ray, but these changes may take several years to develop. AS has been classified according to the modified New York criteria dating from 1984 (Table 2) (Linden et al. 1984), but these criteria do not capture patients in the early stages of the disease (nr-axSpA). The availability of magnetic resonance imaging (MRI) has dramatically improved the imaging of sacroiliitis and promoted the early diagnosis of axSpA. The latest classification criteria formulated by the Assessment of SpondyloArthritis International Society (ASAS) in 2009 state that for the diagnosis of axSpA, radiographic changes are not essential if other findings (HLA-B27 and at least two clinical features typical of axSpA) are present in a patient with (>3 months) back pain and the onset of symptoms before the age of 45 (Rudwaleit et al. 2009a). However, the classification criteria are not the same as the diagnostic criteria, and in

conditions similar to those in Finland, the diagnosis of axSpA should be based on imaging findings at least if anti-rheumatic medication is planned. HLA-B27 negative and MRI-negative nr-axSpA may be considered in those cases where the patient has another comorbidity, such as PsA or IBD.

Figure 1. The current concept of spondyloarthritis (Proft and Poddubnyy 2018).

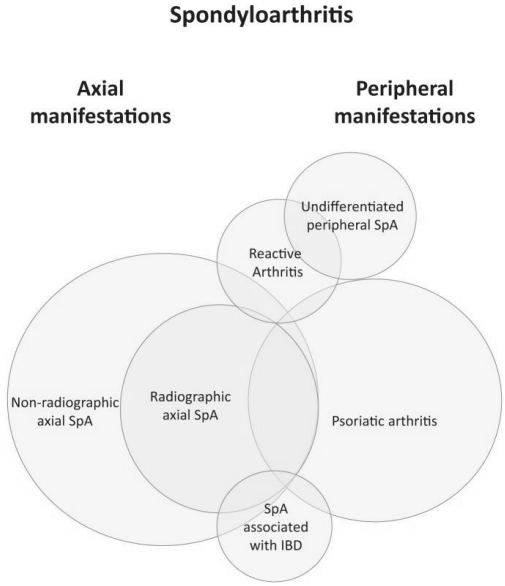
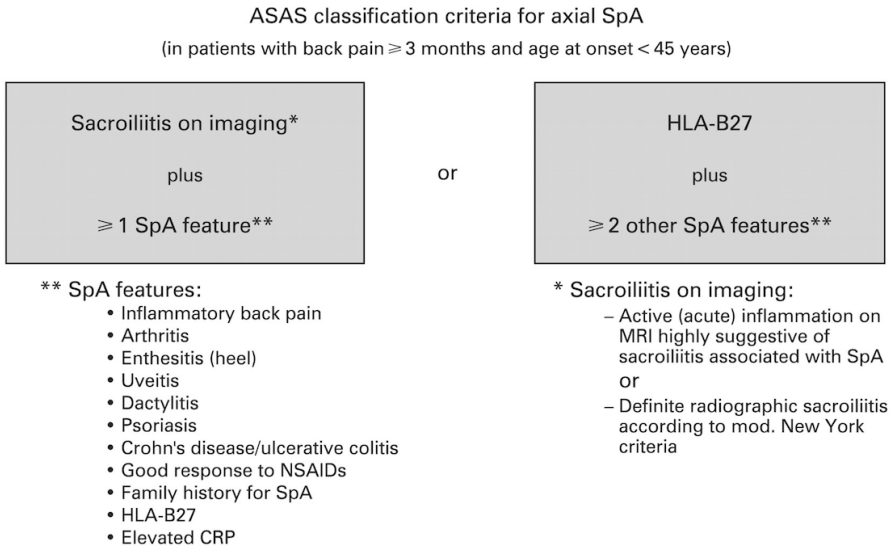


Table 2. Modified New York criteria for classification of ankylosing spondylitis (AS) (modified from Linden et al. 1984)

Clinical criteria
Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest.
Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
Limitation of chest expansion relative to normal values corrected for age and sex.
Radiologic criterion
Sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3-4 unilaterally
→ Definite AS if the radiologic criterion is associated with at least one clinical criterion

Figure 2. The 2009 classification criteria for axial spondyloarthritis by the Assessment of Spondyloarthritis International Society (ASAS) (Rudwaleit et al. 2009a)



2.1.4 Other IAs

Differential diagnosis between IAs is not always simple, and also the classification criteria of distinct IAs have changed over time. Although the main focus of this thesis is on RA, UA, and axSpA, it is worth mentioning a few words on PsA, ReA, SLE, polymyalgia rheumatica (PMR), SS, and undifferentiated connective tissue disorder (UCTD), since they are covered in the incidence section of this thesis.

Psoriatic arthritis is a long-term IA that is often characterized by asymmetric oligoarthritis (inflammation affecting 2-4 joints), dactylitis, tenditis, enthesitis, typical psoriatic skin lesions, and nail changes. Axial involvement may also be present (Ritchlin et al. 2017). Classification Criteria for Psoriatic Arthritis (CASPAR) may be used to assist in the diagnosis, although these criteria were initially formulated for research purposes (Taylor et al. 2006).

ReA is usually triggered by an intestinal infection or sexually transmitted disease. The majority of patients are HLA-B27 positive. ReA is typically self-limiting, and it may stay undiagnosed (García-Kutzbach et al. 2017).

SLE is a chronic and complex autoimmune disease in which disturbances in the immune system lead to organ damage and variable clinical features. The latest

ACR/EULAR classification criteria for SLE were developed in 2019 (Aringer et al. 2019).

PMR is also considered an inflammatory disease that is characterized by the subacute to acute onset of widespread aching, stiffness, and pain especially in the proximal muscles, elevated acute phase reactants, and a good response to GCs. The ACR/EULAR classification criteria for PMR are from 2012 (Dasgupta et al. 2012). SS is a systemic autoimmune disease characterized by chronic lymphocytic inflammation and hypofunction of the exocrine glands, dryness of the mucous membranes, and sometimes extraglandular manifestations. It may occur with another autoimmune disease, such as RA. The latest ACR/EULAR classification criteria for SS are from 2016 (Shiboski et al. 2017). UCTD is diagnosed when there is clinical and/or serological evidence of an existing systemic autoimmune condition which does not meet the criteria for any specific connective tissue disease.

2.2 Epidemiology of IA

The incidence and prevalence figures for IA are affected by methodological differences, such as the study design (e.g. cohort study, cross-sectional study, case-control study, or ecological study) and the case definition/classification criteria applied, thus comparing epidemiological studies from different countries is challenging. In Finland, the total incidence of IAs was estimated to be 142/100,000 in 2010. This study was performed in the Northern Savo area with a population of 206,441, and it identified 292 adult arthritis cases (Kononoff et al. 2017). In other previous estimates from Finland, the Kuopio Arthritis Survey in 2000 and the Heinola Town Case-finding study in 1974, the incidences were 271 and 218/100,000, respectively (Savolainen et al. 2003, Isomaki et al. 1978). In Sweden, the IA incidence was 115/100,000 at the turn of the millennium (Söderlin et al. 2002).

2.2.1 RA

Globally, the estimated age-standardized incidence rate of RA is 14.9/100,000, this figure being mainly based on modelling, as very few countries have true population-based data available (Safiri et al. 2019). Population-based studies have shown high RA incidence rates in the northern hemisphere: Canada (54/100,000), USA

(41/100,000), and Sweden (41/100,000) (Widdifield et al. 2014, Myasoedova et al. 2020, Eriksson et al. 2013); but somewhat lower in the Mediterranean region, such as in Spain (20/100,000), and in the southern hemisphere, like in Argentina (19/100,000)(Di et al. 2016, Fina-Aviles et al. 2016). The RA incidence has also been shown to be lower in rural areas compared to urban areas (Smolen et al. 2016a).

A previous Finnish study based on drug reimbursement data collected patients from 5/21 central hospital districts (population base of approximately 1 million adults) and found a total of 321 patients who satisfied the 1987 ACR classification criteria for RA. This study estimated an overall RA incidence of 29/100,000 (37 among women and 21/100,000 among men) in 2000 (Kaipiainen-Seppänen et al. 2006). In another study from Finland also based on drug reimbursement data but covering the whole population, the respective numbers were 44/100,000 (59 and 30/100,000) between 2000 and 2007. In this study, the case definition was based on the clinical diagnosis of RA by a rheumatologist and the need to initiate anti-rheumatic medication rather than on the fulfilment of the ACR criteria (Puolakka et al. 2010).

Since 1990, the worldwide overall age-standardized incidence rate of RA has risen by 8.2% (Safiri et al. 2019). Population-based studies from the USA and Denmark have also indicated a rising trend (Myasoedova 2010, Pedersen 2007). However, there have been several reports from western Europe, the USA, and Japan of declines in RA incidence, especially during the second half of the 20th century (Hochberg 1990, Jacobsson et al. 1994, Gabriel et al. 1999, Scichikawa et al. 1999, Doran et al. 2002, Kaipiainen-Seppänen 2006), but also following the turn of the millennium (Abhishek 2017). These studies could not provide clear explanations for the trends reported, but environmental factors were speculated to play possible roles. In a previous Finnish study, the incidence of seropositive RA remained stable between 2000 and 2007, while that of seronegative RA decreased (Puolakka 2010). In a US study based on a population cohort from Olmstead county, Minnesota, in which the case definition was based on the fulfilment of at least four of the 1987 ACR criteria for RA, the incidence of RF-negative RA increased, whereas the incidence of RF-positive RA decreased between the RA cohorts in 1995-2004 and 2005-2014 (Myasoedova et al. 2020).

Globally, there were nearly 20 million prevalent RA cases based on modelled data in 2017. The age-standardized RA prevalence rate was 247/100,000, and the rate increased by 7.4% between 1990 and 2017 (Safiri et al. 2019). However, significant

variations between different countries were observed. In the Nordic region, the absolute number of prevalent RA cases increased by 16% due to population aging and growth between 1990 and 2015 according to the Global Burden of Disease Study 2015. The age-standardized RA prevalence declined, but it was higher in the Nordic region compared to the global average in 2015 (0.44% vs 0.35%) (Kiadaliri et al. 2018).

2.2.2 UA

Estimated incidence rates for UA in Finland have ranged from 39 to 149/100,000 (Savolainen 2003, Kononoff 2017) and the reported estimate from Sweden is 41/100,000 (Söderlin 2002).

2.2.3 AxSpA

Since MRI has not been available previously and the whole concept of nr-AxSpA is rather novel, generally only AS is covered in earlier incidence studies; thus, little is known about the incidence rates for nr-axSpA or the whole axSpA population. In Finland, the reported AS incidences lie around 7/100,000 (Savolainen et al. 2003, Kononoff et al. 2017, Kaipiainen-Seppänen et al. 1997), whereas worldwide, the AS incidences range from 0.5 (Japan) to 15/100,000 (Canada) (Hukuda et al. 2001, Bakland et al. 2005, Haroon et al. 2014). The variable results may be explained, e.g. by the prevalence of HLA-B27 in the population, the mean age of the population, and differences in study methods. HLA-B27 prevalence is frequent in individuals of Scandinavian and Inuit origin, and low amongst Japanese, sub-Saharan African, and Australian Aboriginal individuals (Brown et al. 2016). In Finland, HLA-B27 is found in approximately 15% of the population.

An increasing incidence and prevalence of AS was reported in a Canadian study between 1995 and 2010, and this increase occurred at higher rates in women compared to men in recent years (Haroon 2014).

The estimates of AS prevalence (from 36 eligible studies) for each of the major global continents were reported by Dean et al. The mean AS prevalence per 100,000 was 319 in North America, 238 in Europe, 167 in Asia, 102 in Latin America, and 74 in Africa. The estimates of the number of AS patients in Europe were 1.30-1.56

million (Dean et al. 2014). There is limited literature regarding nr-axSpA epidemiology. US data have suggested that axSpA is approximately twice as common as AS; among randomly selected patients (aged 18-44) with chronic back pain and meeting the ASAS criteria, the national prevalence of axSpA was estimated to be 700/100,000, subdivided into prevalences of 350/100,000 for AS and 350/100,000 for nr-axSpA (Strand et al. 2013). Further, some reports have shown that approximately 20-30% of nr-axSpA cases progress to AS in 8-15 years based on findings in plain radiographs (Bakland et al. 2013, Wang et al. 2016).

2.2.4 Other IAs

Worldwide, the incidence of PsA has increased in recent years; it has varied from 0.1 to 41/100,000 in studies from Japan, Norway, Argentina, France, the US, and Sweden (Hukuda et al. 2001, Hoff et al. 2015, Soriano et al. 2011, Pina Vegas et al. 2020, Wilson et al. 2009, Söderlin et al. 2002). Estimates from Finland have ranged from 6 to 23/100,000 (Savolainen et al. 2003, Kononoff et al. 2017, Kaipiainen-Seppänen 1996).

Since ReA is commonly self-limiting and may remain undiagnosed, the estimation of its incidence is challenging. The reported rates lie between 0.6 to 9/100,000 (Savolainen et al. 2003, Kononoff et al. 2017, Hanova et al. 2010, Townes et al. 2008).

The incidence of SLE range from 2 to 7/100,000 worldwide (Elfving 2014, Hermansen 2016, Somers et al. 2014), and previous studies have shown both growing (Uramoto et al. 1999) and stable (Hermansen et al. 2016) trends in its incidence.

PMR is often treated by general practitioners rather than rheumatologists, so its incidence is difficult to study. The disease is probably among the most common IAs; in a population-based US study, the incidence was 64/100,000 (Raheel 2017). The incidence of SS varies markedly worldwide, from 6 to 12/100,000 (See et al. 2013, Elfving et al. 2016, Maciel et al. 2017). The reported incidence of UCTD was 14/100,000 in Finland in 2010 (Elfving et al. 2016).

2.3 Aetiopathogenesis of IA

2.3.1 RA

In RA, an autoimmune reaction causes inflammatory processes targeting the synovial membranes, leading to the formation of inflammatory tissue (pannus), which attacks the adjacent cartilage and subchondral bone, and further results in bone erosions, irreversible damage mediated by osteoclasts, and the loss of function of the affected joint. It has become evident that genetic, epigenetic, and environmental factors contribute to its development (Smolen et al. 2016a).

RA has a hereditary susceptibility; there is a concordance rate of up to 60% based on twin studies (MacGregor et al. 2000). More than 100 risk loci for RA have been found in a genome-wide analysis (Messemaker et al. 2015). Of these, the strongest genetic association lies within the HLA locus containing the HLA-DRB1 gene alleles. The term "shared epitope" (SE) refers to a certain five amino acid sequence motif that is encoded by these HLA-DRB1 alleles, and it has been associated with ACPA-positive RA, whereas other, non-SE coding alleles have been associated with ACPA-negative RA (Lee et al. 2004).

Citrullination of self-proteins, a posttranslational enzymatic process in which the arginine amino acid is converted to citrulline, most likely occurs already before the development of RA begins and is induced by smoking and perhaps also by some other factors. Citrullinated self-peptides have a binding specificity for SE alleles and will then be presented to the immune system, leading to the activation of autoreactive T-cells. Also, other protein modifications, such as carbamylation, have been described in RA patients (Lin et al. 2020).

Dendritic cells take up and present antigens (e.g. citrullinated and carbamylated antigens) to T cells, which start differentiating and producing cytokines, some of which activate B cells into secreting autoantibodies, like ACPA and RF. Autoantibodies associated with RA are detectable several years before disease onset (Wegner et al. 2010), and of these, ACPAs are the most specific serological markers of RA. In a prospective observational cohort, half of all ACPA-positive individuals with new non-specific musculoskeletal symptoms developed clinical arthritis with a median time of 7.9 months (Rakieh et al. 2015). Also, concomitant presence of RF in ACPA-positive patients may further increase the risk of arthritis development

(Bos et al. 2010). ACPAs are associated with joint erosions (Kleyer et al. 2014), increased CV-related and all-cause mortality (Ajeganova et al. 2016), and an elevated risk of RA-related interstitial pulmonary disease in RA patients (Zhu et al. 2014).

The important proinflammatory cytokines are tumour necrosis factor alpha (TNF-α), interleukin (IL) -6, and IL-1. They maintain chronic inflammation and lead to tissue destruction, and they are targeted in RA therapies (Lin et al. 2020).

Smoking is the most generally recognized risk factor for RA, especially for seropositive RA in men (Sugiyama et al. 2010). The association between smoking and ACPA has been shown to be most evident in RA patients who have SE (Hedström et al. 2019). Obesity has also been recognized as a risk factor for RA regarding smoking status (Crowson et al. 2013). A positive correlation between obesity and ACPA-negativity, especially in women, has been shown (Wesley et al. 2013). Also, several other environmental factors, e.g. infections like periodontitis (Chou et al. 2015), pregnancy (de Man et al. 2008), and some dietary factors have been suggested as possible risk factors for RA.

2.3.2 AxSpA

AxSpA is characterized by bone and cartilage loss in the axial skeleton and SI joints, and enthesis followed by subsequent remodelling with new bone formation. Also, peripheral joints and entheses can be affected. The pathogenesis of axSpA is known to be multifactorial; and it includes genetic factors, the intestinal inflammation and gut microbiome, innate-like lymphoid cells, and biomechanical stress in the synovium and entheses. AS and nr-axSpA have been thought to be closely related to each other in their pathogenesis (Baeten et al. 2013).

The genetic susceptibility of axSpA is associated with HLA-B27; however, the mechanism behind this association has not been completely resolved and its presence is not essential (Powis et al. 2016). Also, several non-HLA genes are identified as having links with axSpA (Brown et al. 2016).

Microscopic intestinal inflammation has been demonstrated in 40-60% of AS patients (Mielants et al. 1988, Leirisalo-Repo et al. 1994, van Praet et al. 2013) who are also at an increased risk of developing IBD (Stolwijk et al. 2015). Greater AS disease activity, more pronounced bone marrow oedema of the SI joints in nr-axSpA, and the greater risk of the development of nr-axSpA to AS has been linked

with active gut inflammation (van Praet et al. 2013, Klingberg et al. 2017, van Praet et al. 2014).

Also, the gut microbiota composition in stool samples of SpA patients has been shown to differ from those of both RA patients and healthy controls (Breban et al. 2017). In ileal biopsies of HLA-B27 positive AS patients, the gut epithelial Paneth cells are activated and the mucosal barriers damaged (Ciccia et al. 2017). This structural damage allows the passage of microbiota or their metabolites into the submucosa and the systemic circulation, which further causes different types of cells in the intestine (e.g. innate-like immune cells) to produce pro-inflammatory cytokines (Mortier et al. 2018). After being activated in the gut, innate-like immune cells are capable of migrating from the gut to the entheses and joints, causing inflammatory processes in the tissues (Ciccia et al. 2015).

The most important proinflammatory mediators in axSpA are cytokines IL-17A and TNF-α (Tahir 2018, Kalliolias and Ivashkiv 2016, McGonagle et al. 2019). These mediators, as well as cyclo-oxygenase (COX) enzymes that are responsible for the production of prostaglandins (Ricciotti and FitzGerald 2011), are targeted in the currently used drug therapies for axSpA. Although cytokine IL-23 plays an important role in IL-17A production in many cells, treatment with anti-IL-23 antibodies have not shown to be effective in axSpA (Deodhar et al. 2019a).

In axSpA, the inflammatory processes affect certain anatomical regions more than others, mostly those that are subjected to mechanical stress. Biomechanical stress in the synovium and entheses is sensed by mesenchymal cells, leading to the translation of biomechanical forces into biochemical signals like chemokines, which, in turn, initiate local inflammation and bone destruction (Cambré et al. 2018). Unlike in RA, where the radiographic progression is mainly due to bone resorption and thus erosions, in axSpA the radiographic progression is primarily due to new bone formation. In the entheses, axial inflammation mediated by IL-17 and TNF-α activate the osteoclasts, leading to bone loss. This process is followed by new bone formation of the spine by the development of syndesmophytes, which can, in the worst scenario, bridge across multiple vertebrae and cause a complete fusion of the bones of the spine (bamboo spine) in advanced cases of AS (Poddubnyy and Sieper 2017).

Smoking has been shown to be a predisposing factor for both axSpA incidence and subsequent structural damage caused by the disease (Videm et al. 2014, Dougados et al. 2016). Obesity has also been linked to axSpA (Maas et al. 2016).

2.4 Assessment of IA

2.4.1 RA

A commonly used measure of disease activity in RA is the Disease Activity Score assessing 28 joints (DAS28) (Prevoo et al. 1995). It includes 28 tender and 28 swollen joint counts, the patient's reported visual analogue scale (VAS) for global health (Patient Global Assessment; PGA), and the erythrocyte sedimentation rate (ESR) or sometimes C-reactive protein (CRP) instead of ESR. The DAS28 score is calculated by using these numbers in a complex mathematical formula. A result less than 2.6 implies remission, less than 3.2 low disease activity, and greater than 5.1 the active disease. High pain sensitization even in the absence of synovitis may have an impact on the patient's reported components (tender joint count, VAS for global health), and thus cause a misleadingly high DAS28 score. On the other hand, in cases where RA affects mainly the feet (these are not included in the 28-joint count) or the blood inflammation markers are normal even if the disease is active, the DAS28 score may be misleadingly low.

Other disease activity indices include the simplified disease activity index (SDAI) and clinical disease activity index (CDAI). Both of these include 28 swollen and 28 tender joint counts as well as the patient's and physician's global health assessment (using a 100 mm VAS). SDAI also includes CRP. The values of all components are added together, thus the range of the CDAI is from 0 to 76, and that of SDAI from 0.1 to 86 (Anderson et al. 2011).

The valid definition of RA remission in clinical practice is the nonexistence of swollen (and tender) joints, normal inflammatory markers, and no radiological progression (Mäkinen et al. 2005).

The 1981 ACR criteria for remission require that the patient meets the following: morning stiffness less than 15 minutes, no fatigue, no joint pain, no joint tenderness or pain in motion, no swelling in the joints or tendon sheaths, and a normal ESR for at least two months (Pinals et al. 1981). In the FIN-RACo study, a modified version of these 1981 ACR remission criteria were used; no swollen or tender joints were allowed, and the fatigue and the duration criteria were excluded (Möttönen et al. 1999).

The latest ACR/EULAR remission criteria for clinical trials were created in 2011 (Felson et al. 2011). These criteria include a Boolean definition and an index-based definition for remission. The former requires a tender and swollen joint count ≤1, CRP ≤1 mg/dl, and PGA≤1 on a 0 to 10 scale. The latter requires SDAI to be ≤3.3 or CDAI to be ≤2.8.

Response measures for RA have been developed to better estimate changes in disease activity over time. These include the ACR20, ACR50, and ACR70 response criteria, with respective improvement levels of 20%, 50%, or 70%, in 5 out of the 7 core set variables (tender joint count, swollen joint count, acute phase reactant, patient's assessment of pain, patient's global assessment of disease activity, observer's global assessment of disease activity, and patient's assessment of physical disability). Of these core set variables, the first two are required and none are allowed to worsen. The EULAR response criteria are based on DAS28 change (van Gestel et al. 1996).

Plain radiographs show the radiological progression of RA, and different scoring methods for quantifying the damage (irreversible erosions typically in the small joints of the hands and feet) have been developed (Larsen et al. 1977, van der Heijde 2000). Nowadays, ultrasound is a widely used tool in everyday clinical practice and allows the detection of synovitis more accurately than clinical examination. Ultrasound is also valuable, e.g. in demonstrating when arthralgia is not caused by inflammation. However, targeting ultrasound remission instead of clinical remission has not been shown to improve remission rates of patients with early RA in a randomized study (Haavardsholm et al. 2016). The availability of MRI has also increased. Bone marrow oedema has proved to be an important MRI finding specific to RA and shown to predict future radiographic progression (e.g. new erosions in plain radiographs) in early RA (Olech et al. 2010, Hetland et al. 2009).

2.4.2 AxSpA

Disease monitoring in axSpA includes questionnaires for the AS Disease Activity Score (ASDAS), Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), and pain, as well as swollen joint counts, spinal mobility, and the assessment of extra-articular manifestations.

The ASDAS combines patient-reported outcomes and C-reactive protein (CRP) (or ESR) into an index to assess disease activity; the active disease is defined by an

ASDAS of at least 2.1 and remission at <1.3 (van der Heijde et al. 2009, Machado et al. 2011). The BASDAI consists of a 0-10 scale measuring overall fatigue, spinal pain, arthralgia or joint swelling, overall pain of the body, and the duration and severity of morning stiffness; a BASDAI level of at least 4 is considered as the active disease (Garrett et al. 1994). BASFI is used to assess the degree of functional limitation in axSpA patients, and it consists of 10 questions that evaluate the patient's ability to cope with activities related to functional anatomical limitations and everyday life (Calin et al. 1994).

Radiographs of the spine show the presence of syndesmophytes and thus may have prognostic value, but spinal radiographs are not used for monitoring (van der Heijde 2017). MRI is used to support the diagnosis of nr-axSpA, but it is not recommended for monitoring symptom-free patients (van der Heijde 2017). The main finding of active sacroiliitis is bone marrow oedema located periarticularly or on subchondral bone surfaces of the sacroiliac joints, usually symmetrically. Two or more of these lesions on the same image or one lesion on two consecutive images are considered as a positive MRI finding (Rudwaleit et al. 2009b). Also, the inflammation of ligaments, tendons, fascia, or capsules at the bone insertion sites are typical for axSpA (enthesitis). However, entesitis or synovitis alone (without oedema in the adjacent bone marrow) is not enough to make a diagnosis. In the spine, the active inflammation may show up in the bone marrow of the anterior or posterior vertebral corners (spondylitis), the cortical plates adjacent to the intervertebral discs (spondylodiscitis), the facet joints, or costovertebral joints. Chronic inflammatory lesions in axSpA include fat depositions, subchondral sclerosis, erosions, and ankylosis of the sacroiliac joints or spine, and also syndesmophyte formation in the spine (Canella et al. 2013). The interpretation of sacroiliac joint MRIs may be challenging: mechanical stress or degenerative changes may be hard to differentiate from inflammatory findings, which may lead to the over-diagnosis of axSpA in patients without inflammation (Jans et al. 2014, Eshed and Lidar 2017). In one study by de Winter et al., 23% of healthy individuals, 13% of frequent runners, 57% of women with postpartum back pain, and 92% of patients diagnosed with axSpA had MRI-positive sacroiliitis according to the ASAS definition (de Winter et al. 2018).

2.5 Drug treatment of early IA

The drug treatment options for IA have evolved enormously during the past decades. As the knowledge of the effects of cytokines and inflammatory cells in the pathogenesis of IAs has increased and the modes of action been better understood, new drugs have been developed. The drug treatment of IA consists of disease-modifying anti-rheumatic drugs (DMARDs), GCs, and in axSpA also NSAIDs, which are discussed separately.

DMARDs act by modifying the underlying disease rather than treating the symptoms. They retard the disease progression and its effects on the joints and other tissues, and maintain remission by reducing the occurrence of flare-ups. They also diminish inflammatory pain, swelling, and overall stiffness by these mechanisms. DMARDs allow for the tapering of GCs while sustaining disease control. Some DMARDs are immunosuppressive in nature and thus increase the risk of serious infections. There are three types of DMARDs: conventional synthetic (csDMARD), biological (bDMARD), and targeted synthetic (tsDMARDS). In addition to these drugs on the market, several other molecules are under investigation for RA treatment (Lin et al. 2020).

2.5.1 Conventional synthetic disease modifying anti-rheumatic drugs (DMARDs)

The class of csDMARDs refer to small molecular mass drugs that are synthesized chemically. This class mainly refers to methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), and leflunomide (LEF). Others include, e.g. azathioprine, aurothiomalate, auranofin, and cyclosporine, but today these drugs are either not manufactured any more or play a minor role in the treatment of rheumatic diseases covered in this thesis and are therefore not discussed further.

MTX is a folic acid antagonist that inhibits several enzymes responsible for nucleotide synthesis and purine metabolism leading to the prevention of cell division, and it also suppresses inflammation by different mechanisms, e.g. by increasing T cell apoptosis and adenosine release, alternating the expression of cellular adhesion molecules, and having direct and indirect effects on cytokine release signalling pathways (Braun et al. 2009). It was first used to treat malignancies at high doses and

psoriasis at low doses, but in the early 1990s it was approved for the treatment of RA also in Finland. MTX has become "the anchor drug" in RA, but is also widely used in other IAs (Braun et al. 2009, Smolen 2016, Singh 2016, Lin et al. 2020). It reduces the development of erosive changes and is especially efficient in peripheral arthritis, enthesitis, and tendinitis, but it is less effective in the axial phenotype of axSpA. MTX is used either orally or subcutaneously, once a week, and both as monotherapy and part of a combination therapy. Subcutaneously administered MTX has been shown to be more effective, with improved bioavailability, and to cause fewer side effects compared to oral MTX (Bianchi et al. 2016). Decreased cardiovascular mortality has been associated with MTX use among RA patients (Westlake et al. 2010). Blood count and liver enzymes must be monitored regularly during MTX therapy. The most common side effects of MTX include nausea, vomiting, diarrhoea, hair loss, and tiredness, and concurrent folate supplementation is used to reduce these adverse effects (Visser and van der Heijde 2009). Contraindications for its use are liver or renal failure, bone marrow depression, lung fibrosis, and pregnancy.

SSZ is a pro-drug that is metabolized into two active components, sulphapyridine and 5-aminosalicylic acid, by intestinal bacteria. These compounds have anti-inflammatory, antibiotic, and immuno-modulatory properties, but the exact mechanisms of action remain unclear (Lin et al. 2020). SSZ is used to treat RA, spondyloarthritis, and also IBD. Before the introduction of bDMARDs, SSZ was one of the few pharmacological options available to patients with axSpA, and it still has its place in the initial treatment of axSpA if peripheral arthritis is present (Fagerli et al. 2014). Adverse effects of SSZ include GI-related side effects, elevated liver enzymes, and hypersensitivity reactions, whereas bone marrow depression, neutropenia, and thrombocytopenia are uncommon but serious side-effects. The blood count and liver enzymes should be monitored regularly during SSZ therapy.

HCQ was first used as an antimalarial drug. However, its anti-inflammatory and immunomodulatory properties have made it a widely used anti-rheumatic drug. It increases pH within macrophage phagolysosomes, and thus hinders antigen presentation and the activation of the immune response (Kumar and Banik 2013). In active RA, it is mainly used in combination with other DMARDs, like with MTX and SSZ, in a so-called FIN-RACo combination. EULAR recommendations consider the benefits of HCQ to be limited, since its anti-rheumatic efficacy is moderate (Smolen et al. 2020). HCQ monotherapy is commonly used in different

systemic connective tissue disorders, such as in SLE and SS. The safety profile of HCQ is preferred and no specific laboratory monitoring is required. Besides being an anti-inflammatory drug, HCQ also has favoured metabolic effects; it has been shown to reduce cholesterol and the risk of incident cardiovascular events (Sharma et al. 2016, Rempenault et al. 2018) and diabetes mellitus (Rempenault et al. 2018, Wondafrash et al. 2020), and it also has antithrombotic effects (Kravvariti et al. 2020). Typical side effects include, e.g. mild gastrointestinal (GI) disturbances, skin rashes, and nightmares, whereas feared retinal toxicity is infrequent. However, HCQ is not recommended for patients with pre-existing maculopathy.

LEF is an immune-modulatory agent, a prodrug, whose active metabolite M1 (teriflunomide) is responsible for its pharmacologic activity (Kumar and Banik 2013). It came to market in the late 1990s for RA treatment (Behrens et al. 2011). Its efficiency in the treatment of axSpA is scant and limited to peripheral arthritis (Haibel et al. 2005a). Typical side effects are nausea, diarrhoea, and elevated liver enzymes. Also, new onset hypertension has been reported among LEF users. Contraindications for LEF treatment are severe immunodeficiency, impaired bone marrow function, and uncontrolled infections (Kumar and Banik 2013). Blood count and liver enzymes are monitored regularly during LEF therapy.

2.5.2 Biological DMARDs

BDMARDs are highly efficient, large protein molecules that came to market in the late 1990s for the treatment of IAs. Since RA is probably the most studied disease in rheumatology, the highest number of bDMARDs are approved for its treatment. In contrast to csDMARDs and tsDMARDs, they are infused intravenously or injected subcutaneously and cannot be administered orally. With prolonged use, the efficacy of protein-based biologics may diminish, partly because of the emergence of drug antibodies. Due to massive investments in research and drug development, as well as the complicated manufacturing process, bDMARDs are much more expensive than csDMARDs, and their high price has been a barrier to their extensive use in some countries. Currently the availability of biosimilars that are copies of original biologic drugs with no clinically meaningful differences in safety and effectiveness compared to originator drugs have enabled bDMARD therapy to be offered at lower costs and have also caused a decrease in the price of originator drugs. Overall, the use of bDMARDs is considered to be safe; the risk of serious

infections seems to be moderately increased but, e.g. the risk of malignancies seems not to be increased compared to csDMARDs in several studies (Sepriano et al. 2020). BDMARDs include TNF inhibitors (TNFis), B-cell depleting agent, T-cell antagonist, and several IL (IL-1, IL-6, IL-17, and IL-12/IL-23) antagonists.

TNFis work by inhibiting the cytokine TNF-α and were the first bDMARDs that came to market 20-30 years ago (Curtis and Singh 2011, Monaco et al. 2015). The first one was intravenously administered infliximab (IFX) in 1999 (Maini et al. 1999), followed by subcutaneously injected etanercept (Weinblatt et al. 1999), adalimumab (Keystone et al. 2004), certolizumab pegol (Smolen et al. 2009), and golimumab (Keystone et al. 2009). IFX, adalimumab, and golimumab are monoclonal anti-TNF-α antibodies, etanercept is a soluble form of the TNF receptor, and certolizumab pegol is a PEGylated, humanized antibody-binding fragment of the anti-TNF-α monoclonal antibody (Mitoma et al. 2018). Approved indications for TNFis are RA, axSpA, PsA, and juvenile RA. Some of the TNFis are also used to treat psoriasis, IBDs and uveitis. The formation of drug antibodies has been reported to be less frequent with etanercept (13%) compared to IFX (83%) or adalimumab (54%) use (Strand et al. 2017), and MTX is often used in combination with TNFis to reduce this drug antibody formation. The risk of tuberculosis seems to be increased with the use of TNFis (Sepriano et al. 2020). In axSpA, TNFis have been shown to slow down the radiographic progression of the disease (Baraliakos et al. 2014, Haroon et al. 2013, Rodriquez et al. 2019).

Rituximab (RTX) is a genetically engineered B-cell depleting agent, a chimeric monoclonal antibody against CD20 positive B-cells (Tavakolpour et al. 2019). It is administered intravenously in hospitals. Of the rheumatic diseases, RTX is approved for RA treatment (mainly seropositive RA) and granulomatosis with polyangitis or microscopic polyangitis.

Abatacept is a recombinant fusion protein that selectively blocks T-cell activation by binding to CD80 and CD86 receptors on antigen-presenting cells, thus it interrupts interaction between T-cells and antigen-presenting cells. Several studies have shown its efficacy both in MTX-naïve RA patients as well as in those RA patients with inadequate response to MTX or TNFis (Blair and Deeks 2017). The response to abatacept therapy has been shown to be greater among ACPA positive RA patients compared to ACPA negative patients (Sokolove et al. 2016). As well as for RA, it is approved for PsA treatment. It can be administered both subcutaneously and intravenously.

IL-1 receptor antagonist anakinra is used to treat RA and adult-onset Still's disease. Its clinical efficacy in RA treatment seems to be modest compared to TNFis (Singh et al. 2009); further, it has not proven to be efficient in axSpA (Haibel et al. 2005b).

IL-6 receptor antagonists tocilizumab and sarilumab are indicated for the treatment of active RA in patients failing or having contraindications for at least one csDMARD. Tocilizumab also has indications for giant cell arteritis and adult-onset Still's disease. They have demonstrated good efficacy and tolerability both as monotherapy (Nishimoto et al. 2009, Burmester et al. 2017) and combination therapy (Singh et al. 2011, Genovese et al. 2015) when initial csDMARD or TNFi therapy has failed. In axSpA treatment they have not shown to be effective (Sieper et al. 2014, Sieper et al. 2015).

Anti-IL-17A monoclonal antibody secukinumab is currently, in addition to TNFis, the only approved bDMARD for the treatment of axSpA (Baeten et al. 2013, Pavelka et al. 2017). Another IL-17A antagonist Ixekizumab, which is used for the treatment of severe psoriasis and PsA, has also proven to be effective in the treatment of axSpA (Deodhar et al. 2019b).

IL-12 and IL-23 inhibitor ustekinumab have primary indications for inflammatory bowel diseases and psoriasis, but have also shown efficacy in the treatment of PsA (Azuaga et al. 2020). Ustekinumab is not effective in axSpA (Deodhar et al. 2019a).

2.5.3 Targeted synthetic DMARDs

Janus kinase (JAK) inhibitors include tofacitinib, baricitinib, upadacitinib, and filgotinib, of which tofacitinib was the first one to be introduced on the market in Finland in 2017. They are the latest drug development for the treatment of RA, and they also have an approved indication for PsA. Further, upadacitinib was recently approved for the treatment of axSpA by European Medicines Agency. They are chemical compounds that affect the JAK-STAT signalling pathway in the cells by binding to JAK kinase and inhibiting its action. Thus, JAK inhibitors simultaneously inhibit the action of multiple cytokines, whereas bDMARDs generally inhibit the action of a single cytokine. Due to its chemical structure, JAK inhibitors are easier and cheaper to manufacture than bDMARDs. A risk of venous thromboembolism has been associated with JAK inhibitors (Sepriano et al. 2020).

2.5.4 Glucocorticoids

Oral GCs like prednisolone or prednisone (PRD) have broad anti-inflammatory and immunosuppressive effects (Spies et al. 2010) and they delay radiologic progression in early arthritis (Kirwan et al. 2007). Especially in RA, they are widely used; in several reports, roughly 50% of patients with established RA are presently treated with oral GCs (Haugeberg 2015). Since they offer the rather rapid relief of inflammatory symptoms, they are commonly used as bridging therapy. In axSpA, their role is scant. When used chronically, GSs have several metabolic side effects such as diabetes, osteoporosis, skin atrophy, weight gain, GI bleeding, infections, and hypertension (Da Silva et al. 2006). Local GC injections are effective, offer the rapid relief of inflammatory symptoms, and prevent the progression of the disease (Kuusalo et al. 2016).

2.5.5 Drug treatment recommendations of early IA

2.5.5.1 RA

Until the early 1990s, the recommendations for RA treatment were bed rest and NSAIDs, and only after the failure of these treatments were DMARDs introduced (Burmester and Pope 2017). Fortunately, the knowledge and the treatment options for RA have grown enormously during the past decades, and today, multiple equally effective drug options are available. Several guidelines for the management of RA have been published internationally (Smolen et al. 2020, Singh et al. 2016, Lau et al. 2015, Brenol et al. 2015).

Currently, all recommendations for RA drug therapy underline the importance of early treatment aiming at remission, or at least at low disease activity, and the key role of MTX. The European League Against Rheumatism (EULAR) released its treat-to-target (T2T) initiative in 2010, and these recommendations have later been updated three times (Smolen et al. 2010, Smolen et al. 2014, Smolen et al. 2017, Smolen et al. 2020). However, the international rheumatology community has not reached an agreement on how remission targeting therapy should be initiated in early RA nor on the role of the initial use of csDMARD combinations. According to the latest 2015 ACR recommendations, RA treatment should be started with MTX if no

contraindications are present, and if remission remains unreachable, combinations of csDMARDs or bDMARDs should be initiated (Singh et al. 2016). The EULAR recommendations call for the initiation of MTX monotherapy, possibly in combination with GCs, in early RA. If MTX is contraindicated, SSZ or LEF can be considered as the first drug of choice. If the treatment target has not been reached by six months and prognostically unfavourable factors such as high disease activity and autoantibodies are present, a bDMARD or JAK inhibitor should be initiated. Initial csDMARD combinations are not recommended in the EULAR guidelines (Smolen et al. 2020). The latest ACR recommendations favour low-dose GCs only for patients with moderate to high disease activity, whereas in the EULAR recommendations, GCs are favoured as a temporary bridging therapy when initiating and shifting DMARDs (Singh et al. 2016, Smolen et al. 2020).

The Finnish guidelines differ from the EULAR recommendations. The latest 2015 update of the national Finnish Current Care Guideline states that in early RA, a so-called FIN-RACo combination, a MTX-based triple therapy of csDMARDs (MTX, SSZ, and HCQ), plus a low-dose oral GC (usually PRD) should be initiated, and all swollen joints injected with GCs (Current Care Guideline). If this strategy does not result in a good response within 3-6 months, proceeding to bDMARDs is recommended. Since JAK inhibitors came onto the market in Finland in 2017, they are not included in the 2015 Current Care Guidelines.

In Finland, the findings of the FIN-RACo and the NEO-RACo trials have had an impact on clinical practice (Möttönen et al. 1999, Rantalaiho et al. 2009, Leirisalo-Repo et al. 2013). The FIN-RACo study in 1999 showed that the FIN-RACo combination in early RA was more effective than monotherapy with one csDMARD. There were no differences in adverse events between groups (Möttönen et al. 1999). Further subanalyses showed that not only the initiation of triple therapy but also the physician's activity and targeted treatment were essential in reaching remission (Rantalaiho et al. 2014). The subsequent Finnish Neo-RACo study showed that addition of a bDMARD (IFX) with the FIN-RACo combination resulted in no additional benefit during a two-year follow-up: the remission rate was 82% in both groups (Leirisalo-Repo et al. 2013).

Nevertheless, the csDMARD triple therapy for RA has proven to work also in international studies. In the tREACH study, triple therapy was superior to an MTX + GC combination after three months, and it reduced the need for bDMARD initiation. At one year, there were no differences in disease activities or radiographic

changes, but the costs of treatment and loss of work ability were lower in the triple therapy group than in the MTX + GC group, mainly due to the need for bDMARD initiation in the latter group (de Jong et al. 2016). In the SWEFOT study, patients who were initially non-responders to MTX monotherapy were divided into two groups: those who were treated with triple therapy and those who received the combination of MTX plus IFX. At two years, the groups did not differ from each other in disease activities, although in the IFX group the remission was reached more rapidly (van Vollenhoven et al. 2012). In the RACAT study, the triple therapy did not prove to be significantly worse than the combination of etanercept + MTX, but etanercept produced slightly more quality-acquired life years (O'Dell et al. 2013, Bansback et al. 2017). To show the superiority of MTX monotherapy, EULAR recommendations have referred to the CareRA study, in which three drug combinations were compared: 1) MTX, SSZ, and PRD step down from 60 mg, 2) MTX and PRD step down from 30 mg, and 3) MTX, LEF, and PRD step down from 30 mg. After two years, there were no differences between the groups in disease activities; however, therapy-related adverse events were less common in group 2, and this outcome was considered to support MTX monotherapy (Stouten et al. 2019). Still, it has been shown in several studies that with MTX monotherapy, only approximately 30% of the patients have low disease activity (van Vollenhoven et al. 2009, Moreland et al. 2012).

If the outcome for the patient is likely to be comparable under either treatment (csDMARD triple therapy vs bDMARD therapy), healthcare expenses may drive the choice. The pharmacy price for one year of FIN-RACo therapy is below €2000, even if subcutaneous MTX is used. The prices of one year of treatment with originator TNFis range between € 10,500-13,000 and with TNFi biosimilars between € 4,300-9,400. JAK inhibitors are more expensive than biosimilars, but when their patents expire, major changes in RA treatment can be expected.

2.5.5.2 UA

Even if no classification criteria for a specific disease are fulfilled, the EULAR recommendations for early arthritis in 2007 advocated initiating a DMARD, preferably MTX, as early as possible for patients at risk of developing persistent and/or erosive arthritis (Combe et al. 2007)). The latest update of the recommendation in 2016 brought no significant changes to these principles (Combe

et al. 2017). The goal of treatment is to achieve clinical remission, which is defined as "the absence of signs and symptoms of significant inflammatory disease activity", as promptly as possible (Smolen et al. 2016b). No particular remission criteria are directly advocated, but it is mentioned that composite scores used in RA (DAS28, CDAI, and SDAI) should be used and the ACR-EULAR remission criteria (Boolean or SDAI) is probably the most stringent. There are no comments on the discontinuation of medication in remission (Combe et al. 2017). No specific early arthritis clinics or distinct treatment recommendations for UA are found in Finland, but the T2T principle has been followed in clinical practice regardless of the diagnosis.

2.5.5.3 AxSpA

The current treatment guidelines by EULAR recommend an active T2T treatment strategy also in axSpA (van der Heijde et al. 2017), since high axSpA disease activity has been shown to result in new syndesmophyte formation (Ramiro et al. 2014, Poddubnyy et al. 2016). However, the desired goal (target) of treatment is not clearly defined in the guidelines but should be a "shared decision between the patient and the doctor" (van der Heijde et al. 2017). The lack of robust evidence in this area is why ACR did not include a strict T2T concept in their guidelines (Ward et al. 2019).

NSAIDs are preferred as the first-line pharmacological treatment, and at least two NSAIDs up to the maximum tolerated dose should be tested over a total of a four-week period, not forgetting the potential side effects. The potential benefits of continuous NSAID use in the prevention of structural damage in the spine remains unclear, thus continuous use of NSAIDs is recommended only for symptomatic patients (van der Heijde et al. 2017). Moreover, in real life, the initiation of chronic NSAID therapy for relatively young patients is not always realistic taking into account the potential side effects of NSAIDs.

Although the efficacy of csDMARDs in axSpA is not well documented (Chen and Liu 2005, Chen et al. 2006, Haibel et al. 2007), they are an option for patients with peripheral arthritis, entesitis, or dactylitis, or in case TNFis are not available. SSZ is recommended over MTX. Also, local GC injections may be considered in case of peripheral arthritis. The role of GCs in axial disease is scant, long-term systemic GC treatment is not recommended but short-term GC treatment with a

high (50 mg/day) dose showed to be efficient in a single short (two-week) trial (Haibel et al. 2014).

According to both the EULAR and ACR treatment guidelines, if NSAIDs are not effective enough or peripheral arthritis does not respond to csDMARDs, bDMARDs should be introduced (van der Heijde et al. 2017, Ward et al. 2019). There is some evidence that early (Maksymowych et al. 2013) or prolonged (Baraliakos et al. 2014, Haroon et al. 2013, Maas et al. 2015) treatment with TNFis may prevent new syndesmophyte formation in axSpA. Also IL-17 inhibitors (IL-17is) have shown promising results in this area (Braun et al. 2016). In the European guidelines, there are certain requirements that justify a bDMARD initiation: elevated CRP and/or the presence of inflammation on an MRI of the SI joints and/or spine, and/or the presence of radiographic sacroiliitis (at least grade 2 bilaterally or at least grade 3 unilaterally according to the modified New York grading). Also, a high disease activity, as defined by ASDAS ≥2.1 or BASDAI ≥4, is required.

In Finland, there are no authorized treatment guidelines regarding axSpA management; however, the judgement of an expert group was published in the Finnish Medical Association Journal in 2014 (Paananen et al. 2014). A try-out with at least one csDMARD (preferably SSZ) is required by the Finnish SII before bDMARDs can be reimbursed (Social Insurance Institution Drug Requirements). MTX is frequently combined with TNFi to prevent drug antibody formation; thus it is often tested before bDMARD initiation in Finland.

The recent results from the EuroSpA registry collaboration showed that the overall one-year TNFi retention was higher among the axSpA patients treated with a TNFi + csDMARD combination compared to those treated with TNFi monotherapy, and the risk of treatment discontinuation was 12-13% higher in the TNFi monotherapy group (Nissen et al. 2020).

The bDMARDs registered for the indication of axSpA include TNFis and an IL-17i, secukinumab (in the US also IL-17i ixekizumab). Either one of these bDMARDs can be the first choice, however, usually a TNFi is selected. In case of the failure of the first TNFi, it is always important to re-evaluate if the diagnosis and the indication for bDMARD was right, and if it was, the options are to either try a second TNFi or to switch to IL-17i. The evaluations of the efficiency of bDMARD therapy should be done after 12 weeks of treatment. Slowly and controlled tapering either by dose or administration frequency reduction is encouraged in the European guidelines if the remission is sustained for at least six months. In clinical practice, the time of

maintained remission before tapering is considered is generally longer than six months due to the fear of flare ups, loss of efficacy after restarting treatment, and the development of anti-drug antibodies. ACR guidelines are against tapering as a standard approach, and they are also against switching the originator TNFi to its biosimilar in adults with stable AS (van der Heijde et al. 2017, Ward et al. 2019).

2.5.6 Implementation of drug treatment in early IA

There is a discrepancy between guidelines encouraging a T2T strategy on the one hand and what actually happens in practice. In one study, even if physicians agreed with the given T2T recommendations, only two thirds of their RA patients were prescribed DMARDs during the first month after diagnosis (Gvozdenovic et al. 2016). Adherence to three of the EULAR 2007 recommendations of early arthritis treatment (Combe et al. 2007) concerning the initiation and early adjustment of DMARDs was investigated in an ESPOIR cohort, and the adherence rate for all three recommendations was found to be only 23% among early arthritis patients (Escalas et al. 2012). Nevertheless, the risk of radiographic progression at one year and clinical progression at two years was lower among the patients whose treatment adhered to given recommendations (Escalas et al. 2012). Factors that may cause suboptimal therapy choices include, e.g. economic reasons (medication costs, differences in insurance coverage), the patient's nonadherence to treatment, and the fear of drug-related adverse effects (Kamal et al. 2006, Wolfe and Michaud 2007).

2.5.6.1 RA

A previous Finnish study showed that the proportion of early RA patients starting triple combination within the first month was fairly low, but it increased from 6% to 16% between 2000 and 2007 (Rantalaiho et al. 2011). The preceding versions of national Current Care Guidelines in 2003 and 2009 did not recommend the initiation of the triple combination as rigorously as the current version. The same study found that initially SSZ was the most frequently prescribed DMARD during the first three months after the diagnosis, but at the end of the study period (2006-2007), the initial treatment was most commonly MTX (69%) and combination DMARDs (53%) (Rantalaiho et al. 2011). In Finland, DMARD initiation for early RA and UA patients

has also been studied in two real-life patient cohorts. The first one included 406 patients (310 RA and 96 UA patients) between 2008 and 2011, and it found that in three months, 20% of the RA patients were using the triple therapy, 33% another MTX-based combination, 36% MTX monotherapy, and 8% another DMARD monotherapy; for the UA patients, the respective percentages were 6%, 28%, 43%, and 17% (Rannio et al. 2016). In the more recent (2011-2014) FIN-ERA cohort of 611 DMARD-naïve early IA patients (506 RA and 105 UA patients), MTX-based combination therapy was initiated in 68% of the patients, and the proportion of the triple combination was 31% (Rannio et al. 2017).

Studies from North America and Europe have shown that the implementation of early DMARD initiation according to the current recommendations is not always optimal. In a Canadian cohort of 24,942 early RA patients in 1997-2006, DMARDs were initiated within a year from the diagnosis to only 21% of patients treated by a general practitioner and to 67% of those treated by a rheumatologist (Widdifield et al. 2011). In a Danish cohort of 1516 early RA patients in 1996-2006, only 21% of the patients received MTX within 90 days; however, another DMARD had been initiated to 13% of the patients (de Thurah et al. 2010). In the US, the DMARD initiation for RA patients during the year following the diagnosis declined from 63% to 56% between the cohorts 2004-2008 and 2009-2012 based on commercial and Medicare claims databases (Bonafede et al. 2012, Bonafede et al. 2018). Another US study based on claims databases discovered that more than half of the 63,101 identified RA patients did not receive DMARD treatment within 90 days from diagnosis (Kern et al. 2018). In a study from Canada, only 23% of early RA patients (N=204) were prescribed a DMARD within three months and 47% within six months during 2003-2006 (Jamal et al. 2011). In an Italian cohort of early RA patients (N=1336), the proportion of patients receiving MTX treatment within 3-6 months from the diagnosis was below 40% (Manara et al. 2016).

Better coverages are found if RA patients are treated by rheumatologists. In a review article of studies done in 2002-2013, the penetration of DMARD therapy in cohorts treated by rheumatologists was 77-98% compared to cohorts treated by a mix of physicians (39-63%) (Schmajuk et al. 2013). In the French ESPOIR cohort, at least one DMARD was initiated after a median of four months of disease duration to 77% of early arthritis patients (N=775); the most common choice was MTX (58%), whereas only 6% received combination therapy (Lukas et al. 2009). In a Canadian study of early RA patients (N=339), the proportion of patients with

DMARD therapy within three months from diagnosis was 91%, of those 40% received MTX therapy and 16% combination therapy (Tavares et al. 2011). Further, in a multicentre ERAN cohort in the UK and Eire, the DMARD coverage among RA patients (N=808) was good (97%) and 46% of the patients were on MTX monotherapy; however, the median time of DMARD initiation was eight months after the symptom onset (Kiely et al. 2009). In Italy, a csDMARD was prescribed to 83% of RA patients (N=10,401) at diagnosis, but only 6% of them received initial combination therapy in 2010-2014 (Fakhouri et al. 2018). In a Canadian early arthritis cohort (N=2822) collected between 2007-2017, 79% of the patients received MTX therapy within three months of diagnosis (Moura et al. 2020).

2.5.6.2 AxSpA

Due to differences in healthcare settings, socioeconomic factors, and national guidelines, there are substantial variations in bDMARD prescription patterns in axSpA between countries. Higher country health expenditure has been shown to be associated with greater bDMARD use as well as lower csDMARD uptake (Nikiphorou et al. 2018).

In a study of 3984 patients from 22 countries across four continents fulfilling the ASAS SpA criteria, 38% of the patients were bDMARD users. In a study from the US using a cohort of 775 axSpA patients, 55% of the patients had used bDMARDs at some point, 25% csDMARDs, and 76% NSAIDs (Zhao et al. 2019). However, these studies did not report the disease durations.

A longitudinal observational study from Norway found that of the 724 axSpA patients collected between 2001 and 2012, 25% started with SSZ as their first DMARD after a median disease duration of 2.5 years, whereas 75% started a TNFi as their first DMARD after a median of five years of disease duration. Of the SSZ group, 36% patients later switched to a TNFi, and the median disease duration at that point was also five years (Fagerli et al. 2014)

In a Finnish study of 2890 incident AS patients between 2000 and 2007, 94% of the patients had at least one DMARD purchase, and of these 98% started with DMARD monotherapy, most often with SSZ (87%)(Relas et al. 2014a). The majority of AS patients were able to use SSZ monotherapy for a long median survival time (4.5 years), indicating that SSZ may delay the need for bDMARDs by several years (Relas et al. 2014a). Another study by Relas et al. identified 176 incident AS patients

at Helsinki University Central Hospital between 2005 and 2009, and found that 94% of the patients initially started a csDMARD, most frequently SSZ (95%), whereas bDMARDs were later initiated to 17% of the patients during the mean follow-up time of 3.8 years (Relas et al. 2014b). Compared to the other Nordic countries, the prevalent and incident bDMARD use between 2010 and 2016 was the lowest among Finnish AS patients (Glintborg et al. 2018).

2.6 Pain in IA

Chronic pain is common in various IAs, even after inflammation is adequately suppressed by DMARDs (Roche et al. 2003, McWilliams and Walsh 2016, Ward 1999, Arends et al. 2017). RA patients consider pain relief the most important area of health improvement, and it is also their most common motive to seek medical consultation (Heiberg and Kvien 2002, Lee 2013). More than 80% of AS patients suffer from different levels of pain (Ward 1999). Alongside high disease activity and poor function, widespread pain is one of the factors independently associated with poor quality of life in patients with axSpA (Macfarlane et al. 2020).

2.6.1 Mechanisms of pain

Pain in IA may be multifactorial and caused by different overlapping pain mechanisms, including inflammation, mechanical causes (e.g. structural changes or irreversible degeneration of the joints or spine), and central sensitization (Lee et al. 2011a, Borenstein et al. 2017, Bidad et al. 2017, Blachier et al. 2013). Inflammatory and mechanical causes are likely to cause more localized pain, whereas central sensitization often results in chronic widespread pain and has been shown to play a significant role in IA (Baraliakos 2018, Meeus 2012). Fibromyalgia is a distinct disorder with chronic widespread musculoskeletal pain, but it is also a common comorbidity in patients with chronic pain conditions such as RA and AS (Yunus 2012, Baraliakos et al. 2018).

Thus, pain in IA does not always correlate with inflammation or radiographic measures of disease, and suppression of inflammation by adequate anti-inflammatory therapies may not alone eliminate the pain (McWilliams and Walsh 2016, Blachier et al. 2013, Krabbe et al. 2019, Wu et al. 2015). It has been shown that

pain persisted in 40-50% of RA patients still after one year of DMARD initiation (McWilliams and Walsh 2016). In one study, 40% of axSpA patients still experienced persistent pain after seven years of TNFi treatment (Arends et al. 2017).

However, inflammation plays an important role in centrally-controlled pain mechanisms. Local inflammation in the peripheral joint, synovitis, produces different cytokines (e.g. TNF-α, IL-1, IL-6, IL-17) and other neuromodulatory factors (e.g. kinins and neuropeptides), which can sensitize the peripheral nerves involved in pain perception (McWilliams and Walsh 2017, Bidad et al. 2017). When these sensitized nerve endings (nociceptors) encounter specific noxious stimuli, such as mechanical, chemical, or thermal stimuli, the response in the nervous system may be much stronger than normally (Meeus et al. 2012). Chronic inflammation may cause sustained nociceptive input leading to continuous peripheral sensitization and changes in central pain processing. Lower pain thresholds, allodynia (pain caused by a stimulus that does not normally provoke pain), and hyperalgesia (increased pain by a stimulus that typically provokes pain) are more present in RA patients compared to controls (Meeus 2012). Central sensitization is caused by the direct effect of cytokines produced by the central nervous system's immune cells, and also by circulating cytokines that may pass the blood-brain barrier (McWilliam and Walsh 2017, Nieto et al. 2016).

It is also known that once central sensitization has been established, it may not be reversed by adequate anti-inflammatory treatments and the suppression of synovitis (McWilliams and Walsh 2017). RA patients with a longer disease duration seem to be more prone to increased pain sensitivity (Leffer et al. 2002), thus its development should preferably be prevented early in the disease course by active treatment.

Neuropathic pain is caused by a lesion or disease of the somatosensory system (Colloca et al. 2017), and it may also be present in IA patients. The examples of underlying causes for peripheral neuropathy in IA patients include different comorbidities (most notably diabetes mellitus), compression (e.g. carpal tunnel syndrome), infections, trauma or nerve damage after surgery, vasculitis (mononeuritis multiplex), alcoholism, cancer, and drug therapy adverse effects (e.g. leflunomide) (McWilliams and Walsh 2017, Colloca et al. 2017). Sometimes it is hard to differentiate between centralized and neuropathic pain, depending upon their definition. In a Danish study, neuropathic pain features were estimated to be present

in over 20% of IA patients using a painDETECT questionnaire, and this was speculated to represent centrally mediated pain (Rifbjerg-Madsen et al. 2017).

2.6.2 Measurements of pain

Instruments to measure pain levels are important, since studies assessing patient responses to treatment often use pain improvement as a primary outcome. However, there are always individual differences in the subjective perception of pain; the experience of pain is dependent on the patient's physiological, emotional, and cognitive states. Also, the patient's gender may affect the experience of pain; females with AS report more pain and functional restrictions even if radiographic progression and the levels of circulating acute phase reactants are lower (van der Horst-Bruinsma et al. 2013, Lee et al. 2007).

In RA, pain is usually assessed using a 100 mm VAS, a horizontal line in which 0 corresponds with no pain and 100 with the worst imaginable pain (Scott and Huskisson 1976). More profound tools, such as the McGill pain questionnaire, can also be used (Main 2016). In addition, disability (HAQ, WOMAC) and quality-of-life (SF-36) measures may be useful. In axSpA, pain is assessed using patient-reported outcomes, most commonly in the form of questionnaires, such as BASDAI. Different screening tools, such as the Pain DETECT questionnaire, have been developed to identify neuropathic pain features (Freynhagen et al. 2006).

In recent years, advanced neuroimaging techniques, such as functional brain MRI, electro- and magnetoencephalography, and positron emission tomography have allowed the deeper investigation of the pain mechanisms in the brain and also the measurement of pain responses. Several structural and functional brain MRI abnormalities, such as decreased cortical thickness, diminished brain volumes, and increased levels of excitatory neurotransmitters, have been recognized in patients with chronic pain disorders (Jensen et al. 2013). However, these techniques are too costly for routine clinical practice.

2.6.3 Pain medication

2.6.3.1 Non-steroidal anti-inflammatory drugs

NSAIDS are effective in decreasing pain and swelling and may therefore improve joint function, but they do not prevent joint damage and are thus not disease-modifying (Smolen et al. 2016a). NSAIDs inhibit prostanoid (e.g. prosglandins, thromboxanes, and prostacyclin) biosynthesis through their activity on the COX-1 and COX-2 enzymes.

There are several NSAIDs available, and these include both short-acting NSAIDs (e.g. ibuprofen, diclofenac, ketoprofen, and indomethacin) and long-acting NSAIDs (e.g. naproxen, meloxicam, piroxicam, celecoxib, and etoricoxib). Coxibs are selective COX-2 inhibitors and may reduce GI side effects (Brune et al. 2015). While some coxibs have been withdrawn from the market due to cardiovascular safety concerns, others are still available (celecoxib and etoricoxib).

NSAIDs are considered as first-line analgesics in IA (Lee et al. 2013, Whittle et al. 2012a), but increasing evidence of GI-, cardiovascular-, and kidney-related side effects has reduced their use (Radner et al. 2012, Marks et al. 2012). Therefore, NSAIDs should generally be used on demand with the lowest possible dose and withdrawn after a sufficient response to DMARDs. In active axSpA (with symptoms), however, continuous use of NSAIDs is preferred. Topical NSAID treatment is sometimes an option. The pain-relieving effects of NSAIDs may improve when used in combination with paracetamol; however, adverse effects rise simultaneously (Doherty et al. 2011).

2.6.3.2 Paracetamol

Oral paracetamol (acetaminophen) can be used in the treatment of IA pain if NSAIDs are contraindicated or in combination with NSAIDs, although its efficacy in IA pain is often suboptimal. Paracetamol seems to act through the COX pathway; however, it does not have significant anti-inflammatory effects. It also has central analgesic effects by activating descending serotonergic pathways and influencing cannabinoid receptors (Koes et al. 2020). Its therapeutic range is rather narrow, and

a risk of hepatotoxicity occurs at high doses. The dose of paracetamol should be divided into 3-4 doses and not exceed 3-4 g per day.

2.6.3.3 Opioids

Opioids act in both the central and peripheral nervous system, on receptors (mu, delta, and kappa receptors) located on neuronal cell membranes. Opioids produce analgesia by inhibition of neurotransmitter release from the primary afferent terminals in the spinal cord and activation of descending inhibitory controls in the midbrain. The mu receptor is most commonly associated with analgesia, and naturally occurring opioids and medically used opioids alike bind to this receptor (Bovill 1997).

Four different classes of opioids are recognized: the endogenous opioids produced naturally in the body (such as endorphins); natural opioids (also entitled opiates) extracted from the opium poppy (e.g. morphine, codeine); semi-synthetic opioids created from natural opioids (e.g. oxycodone, buprenorphine); and fully synthetic opioids (e.g. tramadol, methadone, fentanyl, and pethidine) (Ahlbeck 2011).

Opioids can also be separated into three groups based on their pain-relieving capacities: mild opioids (e.g. codeine and tramadol), moderate opioids (e.g. buprenorphine), and strong opioids (e.g. morphine, hydromorphine, oxycodone, and fentanyl).

In recent years, the use of opioids for the treatment of chronic non-cancer pain has increased considerably worldwide. Especially in the United States, opioid consumption both from medical prescriptions and illegal sources has reached epidemic levels since the late 1990s and caused several drug-related problems (Volkow and McLellan 2016, Schuchat et al. 2017). The consumption of strong opioids has also increased in several western and northern European countries, although on average, consumption is still remarkably lower in Europe than in the US (Bosetti et al. 2019, Jarlbaek 2019, Muller et al. 2019). In Finland, the total consumption of opioids presented as defined daily doses (DDD)/1000 inhabitants (inh)/day has decreased; it was 16.6 in 2009 and 15.5 in 2015, and it further decreased to 13.9 in 2018. This drop is mainly caused by a decline in the consumption of the most commonly used opioid, the combination of codeine and paracetamol, from 10.3 to 6.4 DDD/1000/inh/day between 2009 and 2018. The next most commonly

used opioids are tramadol and its combinations, followed by oxycodone and buprenorphine (Finnish Medicine Agency). Strong opioids seem not to be a similar problem in Finland compared to some western countries, although their consumption rate has shown a subtle rising trend during recent years, too (1.7 DDD/1000/inh/day for Oxycodone in 2018). Opioid prescription for non-cancer pain is probably controlled more strictly in Finland than in some other countries (Ahomäki et al. 2020). However, even weak opioids are potentially addictive, and they may be used, e.g. in combination with alcohol or other drugs, and therefore should only be prescribed for valid indications. There has been a rising trend in opioid abuse also in Finland (Häkkinen 2015).

Drug-related problems include, e.g. misuse and abuse of prescription opioids, adverse events associated with chronic opioid use, and drug overdose deaths (Volkow and McLellan 2016, Schuchat et al. 2017). Long-term opioid use may paradoxically cause a condition called "opioid-induced hyperalgesia" in which patients are sensitized to acute pain (Lee et al. 2011b). Another opioid-related harmful effect is increased tolerance, in which an increased dose of an opioid is required to achieve the same analgesic effect. Both of these conditions may lead to a greater opioid dose, which in turn can increase side effects (Lee et al. 2011b).

In addition to well-known harm outcomes among RA patients, such as addiction, exposure to opioids has been shown to increase the risk of serious infections linked to hospitalizations (Wiese et al. 2016) and non-vertebral fractures mostly related to falls (Acurcio et al. 2016), and to cause a delay in the initiation of DMARDs for the treatment of RA (Kern et al. 2018).

Current recommendations thus state that opioids should only be used in cases of careful consideration in IA. Opioids may be used periodically in cases of disabling persistent pain even if IA is optimally treated. In this case, a good patient-physician relationship and careful patient selection is required. Also, dependency and other adverse effects should be monitored critically (Whittle et al. 2012a, Whittle et al. 2013). The latest EULAR recommendations for the treatment of axSpA state that opioid(-like) drugs might be considered when the patient does not respond to NSAIDs or DMARDs, or these treatments are not tolerated or are contraindicated (van der Heijde et al. 2017).

2.6.3.3.1 Opioid use among IA patients

Previous studies, mainly from the US, have shown that IA patients are at risk for excessive opioid use. One US study performed at a single medical centre found that RA patients (diagnosed at least 10 years earlier) were more often opioid users than their non-RA comparators; in 2014, the rate of RA patients using any opioid was 40%, and chronic use, defined as prescriptions for ≥60 days within a 6-month period or those individuals using extended use formulations, was 12%, compared with 24% and 4% of those without RA, respectively (Zamora-Legoff et al. 2016). Another US study based on data from the Corrona registry found out that among 33,739 RA patients, the frequency of self-reported chronic opioid use (defined as any opioid use reported during ≥2 clinical visits that occurred once every three months) increased from 7% to 17% between 2002 and 2015 (Lee et al. 2019). A study based on Medicare data between 2006 and 2014 in the US showed that the proportion of regular opioid users, defined as those with ≥3 filled prescriptions or ≥1 opioid prescription filled for at least a 90-day supply for every 12-month period, had slightly declined after 2010, although it was still 41% in 2014 (Curtis et al. 2017). Even higher numbers were shown in an US study based on a large claims database between 2006 and 2014; this study identified 63,101 newly diagnosed RA patients and reported that the proportions of any opioid users and chronic opioid users (those who received ≥180 days' supply of opioid medication during an average of 3.5 ± 2.1 years of follow-up) were 72% and 25% among the patients who received DMARD therapy versus 57% and 19% among those who did not (Kern et al. 2018). Among Australian RA patients (N=3225) who entered the ARAD register (biologic registry) between 2001 and 2015, the prevalence of baseline opioid use was 33%, comprising mostly (26%) of low-potency opioids such as codeine combinations and tramadol (Black et al. 2019). In a German study, any opioid use rate among RA patients (N=3140) ranged from 6% to 33% in 2015 depending on the reported pain levels, these proportions being closer to numbers found in our study (Jobski et al. 2017).

In addition to RA, a few reports have also shown high opioid use among axSpA patients. In a study from the US, 54% of AS patients among the insured adult population used opioids in 2016 (Walsh et al. 2016). Another US study showed that a quarter of the AS patients in the commercial claims database group and more than three quarters of the patients in the Medicaid population were chronic opioid users (defined as ≥90 days of drug supply)(Sloan et al. 2019). One cohort study on patients from the US and Australia reported intermittent opioid use among 21.7% and

chronic opioid use (defined as daily usage of opioids for more than six months) among 9.5% of a total of 706 AS patients (Dau et al. 2018). A large US study compared the use of long-term (defined as cumulative opioid prescriptions dispensed adding up to ≥90 days during the one-year follow-up) prescription opioids between patients with inflammatory rheumatic diseases (RA, SLE, PsA, and AS) and age- and sex-matched patients with hypertension. The patients with rheumatic diseases had higher rates of long-term opioid prescriptions (AS 25%, RA 19%, SLE 16%, and PsA 15%) compared to the matched controls with hypertension (5-6%), and the risk ratio was highest (2.73) among AS patients (Chen et al. 2019a). Opioid use among AS patients has been associated with subjective measures (depression, BASDAI, BASFI) rather than objective measures of disease activity (Dau et al. 2018).

Recent studies from the US have further shown that among patients with multiple arthritis conditions (including different IAs, gout, and osteoarthritis), the prevalence of opioid prescriptions was almost three times higher compared to those without arthritis (Murphy et al. 2020), and the rate of prescriptions during physician visits increased from 17% to 26% between 2006 and 2015 (Santo et al. 2020).

The role of bDMARDs in opioid use has also been studied among IA cohorts. A few studies have found a slight reduction in the proportion of RA patients using opioids after bDMARD initiation (Park et al. 2019, Kawai et al. 2011, Accortt et al. 2017). Recently presented results (in an abstract) from Iceland, however, did not find a reduction in IA patients' opioid consumption by dose after TNFi initiation (Palsson et al. 2020).

Pain and disability are obvious drivers of greater opioid use among RA patients (Black et al. 2019), but several other factors have also been recognized: obesity (Baker et al. 2020); depressive symptoms; antidepressant use (Jobski et al. 2017, Lee et al. 2019, Curtis et al. 2017); other comorbidities, such as cardiovascular disease (Curtis et al. 2017); GC use (Zamora-Legoff et al. 2016, Black et al. 2019); female gender (Curtis et al. 2017, Zamora-Legoff et al. 2016); and younger age (Curtis et al. 2017, Black et al. 2019). In the general population, lower socioeconomic status has been linked to greater opioid use (Hooten et al. 2015, Chen et al. 2019b, Böckerman et al. 2020), but Zamora-Legoff et al. did not find an association between education level and opioid use rates in the RA population (Zamora-Legoff et al. 2016).

2.6.3.4 Neuropathic pain medication

The first-line drugs for the treatment of neuropathic pain include gabapentinoids (gabapentin and pregabalin), serotonin-norepinephrine reuptake inhibitors (duloxetine and venlafaxine), and tricyclic antidepressants (amitriptyline, nortriptyline) (Attal et al. 2010). In some cases, especially in the presence of pain-related sleep disorders or anxiety, neuropathic pain medication can be used as additional pain treatment for IA patients.

2.6.3.5 New drugs for IA pain

Recently, new drugs targeting both inflammatory and neuropathic pain in IA patients have been researched. These drugs include those that target N-methyl-D-aspartate receptors (NMDAR), especially its subunit NR2B (N-methyl-D-aspartic acid receptor 2B) (Noh and Ismail 2020); transient receptor potential cation channel subfamily A member 1 (TRPA1) (Kistner et al. 2016); and microRNAs (Kress et al. 2013).

3 AIMS OF THE STUDY

The aims of the present study were:

1. To estimate the trends in the incidence of IAs in Finland during the 15-year observation period (2000-2014) (study I).

2. To characterize the current use of DMARDs in patients with newly onset RA, UA, and axSpA (studies II and IV).

3. To evaluate the trends in the pain medication use of patients with newly onset RA, UA, and axSpA with a special emphasis on opioid use, and to compare the results to the general population (studies III and IV).

4 MATERIALS AND METHODS

4.1 Background

The current study is purely register-based. The data for this work came from nationwide Finnish registers and statistics, e.g. the Drug Purchase Register, the Reimbursement Register, the Population Register Centre, and Statistics Finland. These registers serve research purposes, although they are mainly maintained for administrative needs.

4.2 Drug Purchase Register

The Drug Purchase Register, maintained by the Social Insurance Institution (SII), was established in 1994. This register covers all drug purchases prescribed by physicians and reimbursed by the National Sickness Insurance Scheme in Finland. The register data include information on drug class, quantity, and date of dispensation. Drugs are categorized according to the Anatomical Therapeutic Chemical (ATC) classification system. To qualify for reimbursement, the drug must be purchased in the most economical package size for a maximum of three months' consumption, although the prescriptions are valid for two years from the day on which they are prescribed. Drugs administered in hospitals, e.g. intravenous IFX, RTX, or belimumab, are not recorded in the register, nor are over-the-counter medicines. Receiving the reimbursement decision is economically very much in the patient's interest. If the reimbursement has not been applied for, the patients are encouraged by a pharmacist to request it.

4.3 Reimbursement Register

The Finnish social security system, organized by the SII, offers all permanent residents in Finland a variety of benefits. The costs of most drugs prescribed by a physician for the treatment of a disease are partly or fully reimbursed by the SII, at basic, lower special, or higher special rate, depending on the disease and its severity. Between 2000 and 2014, the basic reimbursement covered 42% of the drug price, the lower special reimbursement (SR) covered 65-72% of the drug price, and the higher SR covered 100% of the drug price. In order to qualify for SR, a treating physician working in a rheumatology clinic must file a Medical Certificate B, which describes the diagnostic procedures and prescribed medication to the SII. The certificate is then checked by the SII's insurance physician usually within 3-4 weeks, and if the SR decision is awarded, the patient will receive a new personal health insurance card with a respective code. The reimbursements are granted independently of the patient's socioeconomic status and place of residence. Drugs administered in public hospitals and over-the-counter drugs are not reimbursable. SR decisions are recorded in the Reimbursement Register by date of entitlement, ICD-10 code of the disease, and the patient's age and gender.

Patients with chronic IAs can be granted a lower SR for anti-rheumatic drugs. In Finland, the Medical Certificate B is completed routinely at rheumatology clinics on the diagnosis of IA, therefore, practically all patients using DMARDs receive SRs from the SII. However, in those mild IA cases where DMARD initiation is not necessary, at least early in the disease course, the certificate is not completed. Thus, these patients are not included in the Reimbursement Register.

4.4 Patient cohort

The case identification method of this study was based on the SR register data for IA medications. From this nationwide register, all incident patients (aged ≥18 years for studies I, III, and IV, and ≥16 years for study II) granted the first SR for medications of IA during the observation period were collected. This observation period extended from 1 January 2000 to 31 December 2014 for study I, from 1 January 2011 to 31 December 2014 for study II, and from 1 January 2010 to 31 December 2014 for studies III-IV. The patients were identified with ICD-10 codes

[M05 for seropositive RA, M06 for seronegative RA, M13 for UA, M45-46 for axSpA (including AS and nr-axSpA), L40.5 for PsA, M02 for ReA, M32 for SLE, and M35 for a group of diseases including PMR, SS, and UCTD] (Figure 3). IBD-associated arthritis could not be analysed from the register since the majority of the incident patients already had SR for DMARDs on the grounds of their colitis. Some rare rheumatic diseases, such as myositis, scleroderma, and vasculitides, were not included due to the low number of patients with these diseases.

In study IV, the axSpA patients were divided into two groups depending on whether self-injected bDMARDs were initiated after ID (group B) or not (group A) by the end of 2015 (Figure 4). The day of the first reimbursement decision was defined as the index date in this study.

Figure 3. Case identification protocol for studies I-IV.

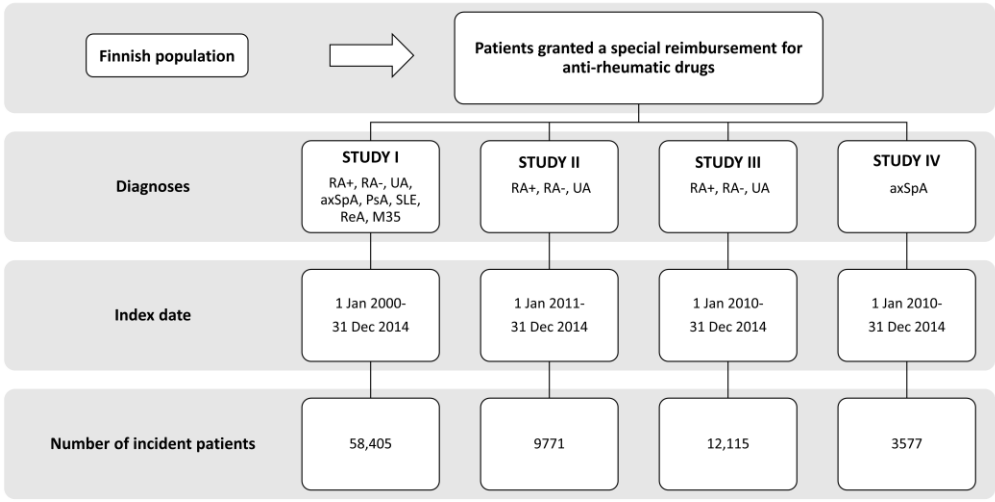
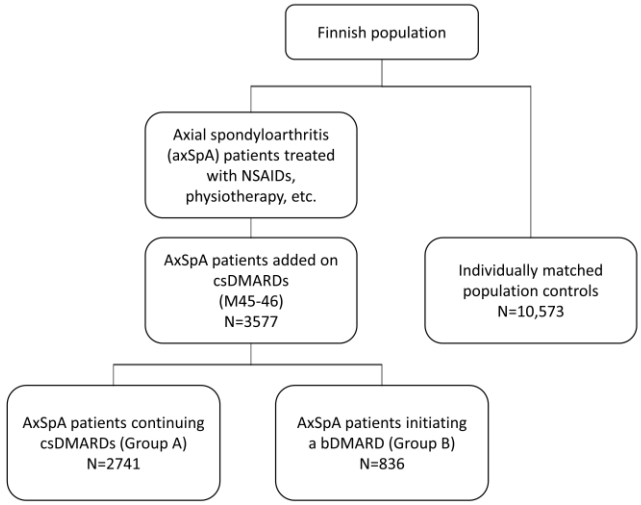


Figure 4. Case identification protocol for study IV.



4.5 Controls

For each incident case, three eligible controls were randomly selected and individually matched according to age, sex, and place of residence by the Population Register Centre (Studies III and IV). Those persons among the controls that had been granted SR for any IA before 2010 were excluded. The number of controls was 35,530 in study III and 10,573 in study IV.

4.6 Drug purchases

Information on dispensed drugs was obtained from the Drug Purchase Register. Data on the patients' csDMARD, GC, and self-injected bDMARD purchases (studies II and IV) as well as the patients' and controls' pain medication purchases (studies III and IV) were collected. CsDMARDs covered MTX, SSZ, HCQ, LEF,

azathioprine, aurothiomalate, auranofin, cyclosporine, and mycophenolate. Self-injected bDMARDs covered TNFis (adalimumab, etanercept, golimumab, certolizumab pegol), and also T-cell inhibitor abatacept (study II) and anti-IL12/23 monoclonal antibody ustekinumab (study IV). Of the pain medications, the main interest was in opioids [mild opioids (codeine combination products and tramadol), moderate opioids (buprenorphine), and strong opioids (morphine, hydromorphine, oxycodone, and fentanyl)], but also the purchases of NSAIDs and paracetamol were analysed.

The csDMARD and self-injected bDMARD purchases were analysed between the years 2011 and 2014 (study II) and between 2010 and 2015 (study IV). Pain medication purchases were analysed starting from 2009 (until the end of 2015) due to the inconsistent reimbursement of codeine combination products (the most frequently used opioid in Finland) before 2009 (studies III and IV).

Opioid, NSAID, and paracetamol purchases were evaluated one year before and after the index date, further dividing the observation time into 3-month periods (studies III and IV). Long-term opioid use was defined as opioid purchases in at least three of these periods per year (studies III and IV). The drug reimbursement regulations of the National Sickness Insurance Scheme restrict the reimbursed drug supply period to a maximum of three months per purchase. All opioids from mild to strong were included. A prescription is mandatory for dispensed DMARDs and opioids. Paracetamol and some NSAIDs are available over the counter in small amounts.

In study IV, the opioid purchase frequencies of group B patients one year before and one year after the initiation of self-injected bDMARD therapy were investigated to study whether the start of a bDMARD had an impact on the amount of opioid use. For this, the defined daily doses (DDDs) described by the World Health Organization (WHO) were used as a tool to assess the opioid consumption one year before and one year after the initiation of a bDMARD. By definition, DDD is the assumed average maintenance dose per day for the main indication of the drug, usually established at the time of marketing; thus it provides a fixed unit of measurement that accounts for the differences in medicine formulations and package sizes and strengths, and it makes national and international comparisons possible at the population level (WHO Collaborating Centre for Drug Statistics Methodology).

Further analyses on whether certain drug purchases (ATC classes N05, N06, and C1-C10) by the IA patients were associated with opioid purchases during the year

after the ID were performed. The ATC class N05 refers to psycholeptics (antipsychotic drugs, anxiolytic drugs, hypnotics, and sedatives), N06 to psychoanaleptics (antidepressants, psychostimulants, psycholeptics and psychoanaleptics in combination, dementia drugs), and C1-10 to different cardiovascular drugs.

4.7 Statistical analysis

In study I, the number of newly diagnosed IA cases was divided by the total number of the population (≥18 years of age) between 2000 and 2014 to calculate the mean annual incidence rates for both genders per 100,000 persons in 5-year calendar time intervals (2000-2004, 2005-2009, and 2010-2014). Patients and the population at risk were stratified by gender and age (18-24, 25-29,…90+), and a Poisson distribution was assumed to calculate crude and direct adjusted incidence rates with 95% confidence intervals (CI). Standardized incidence rate ratios (IRRs) were calculated by using Poisson or negative binomial regression models when appropriate, and the covariates in these models were the patient's age and the calendar year of the index date. The Lagrange multiplier test was used to test the assumption of overdispersion in the Poisson model. An analysis of variance with an orthogonal polynomial contrast was used to evaluate the statistical significance for the hypothesis of linearity across the categories of calendar years (2000-2004, 2005-2009, and 2010-2014) and the patients' age. Population sizes according to gender and age for the calculation of incidence rates were obtained from Statistics Finland.

In the analysis of the use of DMARDs (study II), statistical comparisons between diagnoses were made using the Chi-square test. In the analysis of opioid use (study III), statistical comparisons between the cases and controls were made using the Chi-square test, and generalized linear models with a binomial family and log link. In study IV, continuous variables between groups were compared with the t-test and categorical variables with Pearson's Chi-square test.

In study II, generalized linear models with appropriate distribution and link function were used to identify whether age and gender were associated with the initiation of DMARD therapy (versus no DMARDs) or with the initiation of combination therapy (versus monotherapy) within the first month after the index

date in each diagnosis group separately. In study IV, generalized linear models were applied to estimate odds ratios (ORs) and risk ratios (RRs).

In Studies III, and IV, longitudinal measures of purchasers of opioids and the opioid consumption (DDD) in study IV were analysed using the generalized estimating equations (GEE) model (with appropriate distribution and log link function) with an unstructured correlation structure.

In study IV, the Kaplan–Meier estimation served to illustrate data on the cumulative use of bDMARDs. Cox proportional-hazard models were used to estimate the hazard ratios (HR) adjusted for age, gender, and education level (basic, middle level, lower high level, and upper high level). The data on education levels were obtained from the Population Register Centre (Statistics Finland) (studies III and IV).

The statistical packages used for the analysis of the substudies included in this thesis were Stata 14.1 (study I), Stata 15.1 (study II and III), and Stata 16.0 (study IV), StataCorp LP (College Station, TX, USA).

4.8 Ethical considerations

Approval to use the databases was acquired from the SII. In accordance with Finnish legislation, there was no need to acquire permissions by an ethical committee or informed consent for register-based studies done without contacting the study subjects.

5 RESULTS

5.1 Demographic data of IA cohorts

In study I, 58,405 adult (≥18 years old) patients (64% female) contracted a new IA requiring the use of DMARDs. The mean age [standard deviation (SD)] at the ID was 52 (16) years, range 18 to 96 years. Of these patients, 18,163 (67% female) had seropositive RA, 9784 (69% female) had seronegative RA, 7399 (66% female) had UA, 8396 (48% female) had axSpA, 6702 (49% female) had PsA, 1434 (53% female) had ReA, 992 (84% female) had SLE, and 5535 (81% female) belonged to the group under the ICD-10 code M35.

In study II, altogether 9771 patients (>16 years old) with a new IA diagnosis were identified, 4998 patients with seropositive RA [67% female, mean (SD) age 58(15) years], 2340 with seronegative RA [68% female, 56(17) years], and 2433 with UA [68% female, age 49(17) years].

In study III, a total of 12,115 adult (≥18 years old) patients with seropositive RA, seronegative RA, or UA were identified. Of these, 6186 patients (66% women) had seropositive RA, 2970 patients (67% women) seronegative RA, and 2959 patients (67% women) had UA. The mean ages (SD) at diagnosis were 58 (15), 57 (17), and 49 (17) for seropositive RA, seronegative RA, and UA, respectively.

In study IV, 3577 adult (≥18 years old) axSpA patients (53% female) were identified. The patients were divided into two groups according to the use of bDMARDs (A=no, B=yes) by the end of 2015. Group A consisted of 2741 patients [53% female, mean (SD) age 39(13) years] and group B included 836 patients [49% female, 38(11) years].

5.2 Trends in the incidences of IAs

In the period 2000-2014, the mean yearly number of incident patients with IA increased 12% [95% confidence interval (CI) 9.8-14.3], from 3696 to 4141 between

the first and the last five-year period (Fig. 5A) due to the increased number of people at risk. In the year 2000, the mean yearly number of incident IA patients was 3531 and in the year 2014 it was 4329, thus the increase was 23%. IA was more common in women than in men. In the observed 15-year period, the nationwide mean annual incidence was 115 per 100,000 among women and 70 per 100,000 among men. The age-adjusted mean annual incidence rate of IAs among women increased from 114 [95% confidence interval (CI) 113-118] to 116/100,000 (95% CI 115-120) from 2000-2004 to 2010-2014 with an incidence rate ratio (IRR) of 1.03 (95% CI 1.01-1.06; p=0.008) (Fig. 5B). The respective increase among men was from 69 (95% CI 67-72) to 71/100,000 (95% CI 69-74), and an IRR of 1.10 (95% CI 1.06-1.14; p<0.001). The distribution of different IAs in 2014 is shown in Figure 6.

Figure 5. a) Mean annual number of incident IA patients by sex and 5-year intervals. b) Age-adjusted annual incidence rates of IAs by sex and 5-year intervals (**I**).

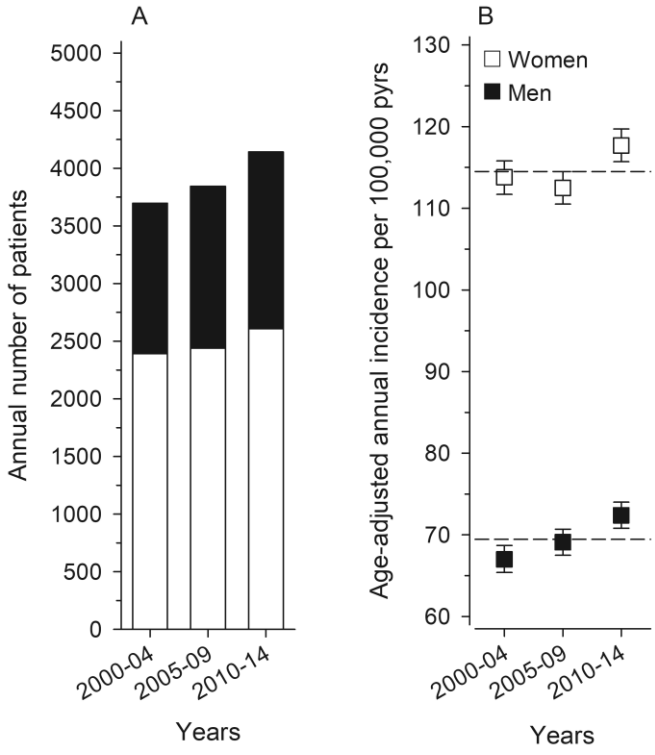


Figure 6. Number of incident IA cases in Finland in 2014 (**I**).

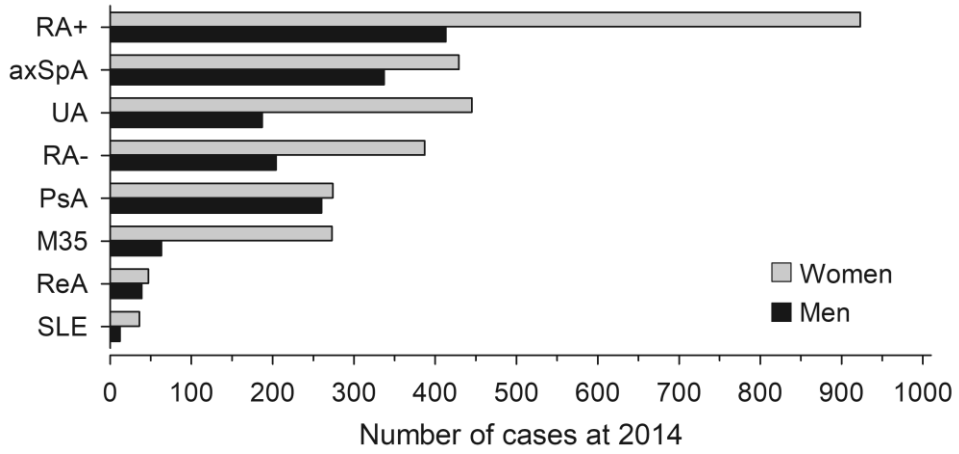


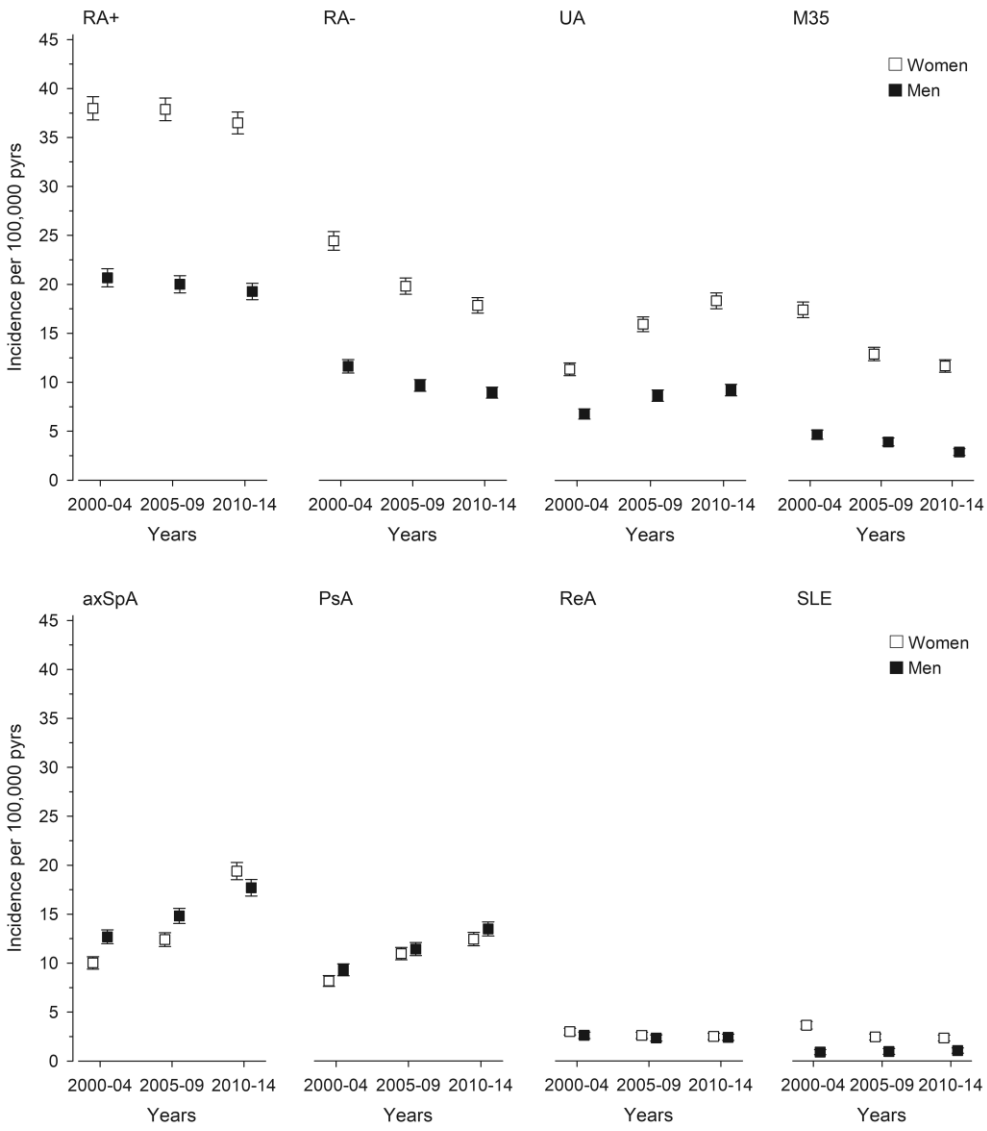
Table 3 shows the annual crude incidence rates and mean ages at the index date for each diagnosis, as well as the statistical significances of linearity for age- and gender-adjusted incidences and mean ages.

The incidences of seropositive RA and ReA did not change significantly (Table 3, Figure 7). The rise in the incidence was observed for UA, axSpA, and PsA, whereas seronegative RA, a group of diseases under the ICD-10 code M35, and SLE showed a declining trend. The gender difference in axSpA levelled off as the incidence in women increased at a higher rate than in men.

Table 3. Total number of incident cases (N), mean annual crude incidence rates per 100,000, and mean ages at diagnosis for various IAs during 2000 to 2014 (**I**).

		Incidence per 100,000				Mean age at diagnosis (SD)			
	N	**2000-04**	**2005-09**	**2010-14**	***P* for linearity**	**2000-04**	**2005-09**	**2010-14**	***P* for linearity**
RA+	18,163	29	30	29	0.055	57 (14)	57 (14)	58 (15)	<0.001
Women	12,159	37	38	37		56 (15)	57 (15)	57 (15)	
Men	6004	20	21	20		58 (13)	59 (13)	60 (13)	
RA-	9784	18	15	14	<0.001	54 (16)	55 (16)	57 (17)	<0.001
Women	6713	24	20	18		54 (16)	55 (16)	56 (17)	
Men	3071	11	10	9		55 (15)	57 (16)	59 (15)	
UA	7399	9	12	14	<0.001	48 (15)	49 (16)	49 (17)	0.12
Women	4896	12	16	18		48 (15)	48 (16)	48 (17)	
Men	2503	7	9	9		49 (15)	50 (15)	51 (16)	
axSpA	8396	12	14	18	<0.001	39 (12)	38 (12)	38 (12)	0.74
Women	4047	11	12	19		39 (12)	39 (12)	39 (12)	
Men	4349	13	15	17		38 (12)	37 (12)	38 (12)	
PsA	6702	9	11	13	<0.001	48 (13)	49 (12)	49 (13)	0.021
Women	3278	8	11	12		48 (13)	49 (13)	49 (13)	
Men	3424	9	12	13		47 (12)	49 (12)	48 (13)	
ReA	1434	3	2	2	0.063	44 (14)	42 (14)	42 (14)	0.028
Women	765	3	3	3		44 (14)	42 (14)	42 (14)	
Men	669	3	2	2		43 (13)	43 (14)	42 (15)	
M35	5535	11	9	8	<0.001	61 (16)	59 (16)	58 (16)	<0.001
Women	4504	17	13	12		60 (16)	58 (16)	57 (16)	
Men	1031	4	4	3		64 (15)	62 (14)	63 (14)	
SLE	992	3	2	2	<0.001	46 (16)	46 (16)	45 (16)	0.26
Women	833	4	2	2		46 (16)	46 (16)	45 (16)	
Men	159	1	1	1		52 (15)	47 (16)	48 (17)	

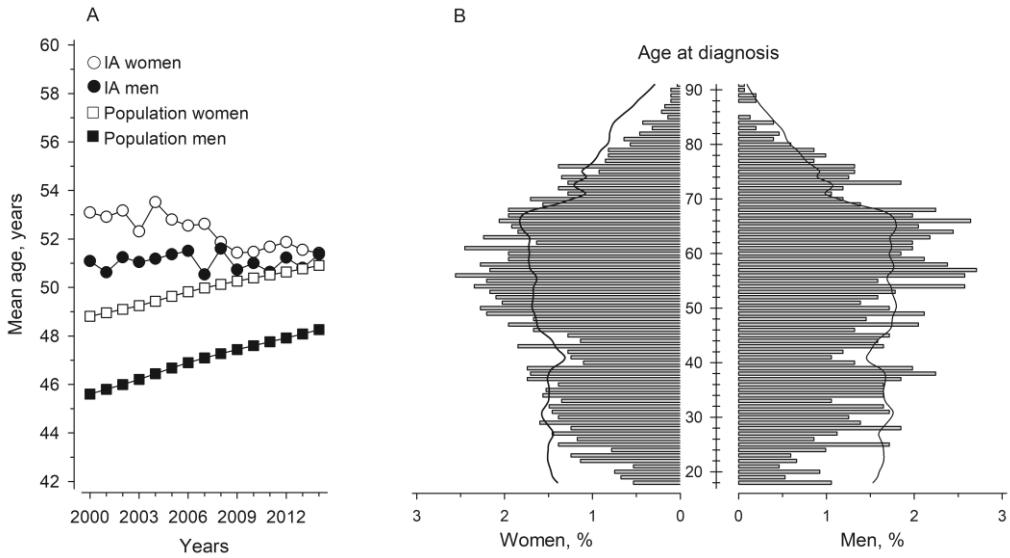
Figure 7. Age-adjusted annual incidence rates by sex for 8 different IAs presented in five-year intervals during 2000-2014 (**I**).



The mean age at diagnosis increased statistically significantly in seropositive and seronegative RA and PsA, and decreased in ReA and M35. No significant changes in the mean ages were seen in UA, axSpA, or SLE (Table 3).

As seen from Figure 8A, the mean age of the Finnish population has risen during the present millennium (data derived from Statistics Finland), whereas the mean age at diagnosis of IAs has slightly declined, especially among women. The age distribution of all patients entitled to an SR for anti-rheumatic drugs as well as the age structure of the general population (according to Statistics Finland) in 2014 are presented in Figure 8B.

Figure 8. a) Mean age at diagnosis of an IA and the mean age of adult population during 2000-2014 in Finland. White dots refer to the mean age of women and black dots to the mean age of men at time of IA diagnosis. White squares refer to the mean age of the general adult female population and black squares to the mean age of the adult male population. b) Age and gender distribution of incident Finnish patients awarded an SR for anti-rheumatic medication in 2014. The black lines indicate the age structure of general population **(I)**.



5.3 DMARD purchases

5.3.1 RA and UA patients

The drugs purchased by RA and UA patients during the first month after the ID are presented in Table 4. All csDMARD combinations were used more commonly by seropositive RA patients compared to seronegative RA or UA patients. Also, the use of MTX and PRD was most common among the seropositive RA group. Any other csDMARDs than MTX, SSZ, and HCQ were rarely used during the first month by the patient groups. Also, the share of self-injected bDMARDs was very low.

During the first year, the proportions of patients purchasing any csDMARDs increased, especially in the seropositive RA group (Table 5). MTX, SSZ, and HCQ remained the most commonly used drugs, followed by LEF; the share of all other csDMARDs was small. Self-injected bDMARDs were initiated most frequently by seronegative RA patients (5.3%), and more rarely by the two other patient groups ($p<0.001$). The proportion of patients with no medication by the end of the first year after diagnosis was only 3% in the UA group and even less than that in the RA groups ($p<0.001$).

The median numbers (interquartile range; IQR) of patients' DMARD purchases by the end of the first year after diagnosis are shown in Table 5. Further, we divided patients into two groups depending on whether they were initially treated with the FIN-RACo combination (MTX+SSZ+HCQ) or not. By the end of the first year after diagnosis, the median (IQR) number of DMARD purchases was 18 (15 to 22) for seropositive RA, 19 (15 to 22) for seronegative RA, and 18 (15 to 24) for UA in the FIN-RACo group, whereas the respective numbers in the non-FIN-RACo group were 10 (6 to 13) for seropositive RA, 9 (6 to 13) for seronegative RA, and 7 (4 to 11) for UA. Thus, patients in the FIN-RACo group had almost twice as many DMARD purchases as the rest of the patients.

In multivariate analyses, using age and gender as covariates, gender did not predict whether DMARDs were initiated or not, or whether the patient was treated with combination therapy or monotherapy during the first month after the index date in any of the three diagnosis groups. Higher age was negatively associated with DMARD initiation within a month from diagnosis among UA patients [OR 0.99 (CI 0.98-0.99)] but not among RA patients. The initiation of combination therapy

decreased with a rising age among seropositive RA patients [OR 0.99 (CI 0.98-0.99)] but not among the other diagnosis groups.

Table 4. Baseline characteristics and the numbers and proportions (%) of DMARD and PRD purchasers among patients with seropositive RA, seronegative RA, and UA by the end of the **first month** after the ID. Also, the used drug combination strategies are shown.

	Seropositive Rheumatoid arthritis	**Seronegative Rheumatoid arthritis**	**Undifferentiated arthritis**	***p*-value**
Number of patients (N)	4998	2340	2433	
Females, N (%)	3349 (67.0)	1584 (67.7)	1650 (67.8)	
Mean age at diagnosis, years (SD)	58 (15)	56 (17)	49 (17)	
Medications				
Methotrexate (MTX)	3602 (72.1)	1483 (63.4)	1043 (42.9)	<0.001
MTX per os	3428 (68.6)	1399 (59.8)	949 (39.0)	
MTX s.c.	174 (3.5)	84 (3.6)	94 (3.9)	
Sulfasalazine (SSZ)	2059 (41.2)	880 (37.6)	1121 (46.1)	<0.001
Hydroxychloroquine (HCQ)	2272 (55.5)	940 (40.2)	472 (19.4)	<0.001
Leflunomide	51 (1.0)	30 (1.3)	23 (1)	0.48
Azathioprine	29 (0.6)	11 (0.5)	14 (0.6)	0.83
Aurothiomalate	9 (0.2)	2 (0.1)	2 (0.1)	0.44
Auranofin	3 (0.1)	1 (0.0)	1 (0.0)	0.95
Cyclosporine	1 (0.0)	3 (0.1)	6 (0.3)	0.015
Prednisolone/prednisone (PRD)	3025 (60.5)	1352 (57.8)	890 (36.6)	<0.001
Self-injected biologics (all)	41 (0.8)	28 (1.2)	17 (0.7)	0.15
Etanercept	3 (0.06)	11 (0.47)	2 (0.08)	
Adalimumab	4 (0.08)	6 (0.27)	1 (0.04)	
Certolizumab	1 (0.02)	0 (0)	0 (0)	
Golimumab	3 (0.03)	1 (0.04)	0 (0)	
Abatacept	1 (0.02)	0 (0)	0 (0)	
No anti-rheumatic medication	401(8.0)	227 (9.7)	300 (13.3)	<0.001
Only PRD	85 (1.7)	63 (2.7)	46 (1.9)	0.61
Combination strategies of DMARDs, N (%)				
Two DMARDs	1684 (33.7)	727 (31.1)	395 (16.2)	<0.001
Three DMARDs	1118 (22.4)	255 (10.9)	77 (3.1)	<0.001
MTX-based combination	2489 (49.8)	841 (35.9)	390 (16.0)	<0.001
FIN-RACo combination*	1114 (22.3)	253 (10.8)	75 (3.1)	<0.001
MTX+SSZ+HCQ+PRD	922 (18.4)	205 (8.8)	52 (2.1)	
MTX+SSZ+HCQ	192 (3.8)	48 (2.1)	23 (0.9)	

*FIN-RACo combination: MTX, SSZ, and HCQ often combined with low-dose PRD

Table 5. Baseline characteristics and the numbers and proportions (%) of DMARD and PRD purchasers among patients with seropositive RA, seronegative RA, and UA by the end of the **first year** after the ID. Also, the numbers of DMARD purchases by the patients during the first year after diagnosis are shown.

	Seropositive rheumatoid arthritis	Seronegative rheumatoid arthritis	Undifferentiated arthritis	*p*-value
Number of patients (N)	4998	2340	2433	
Females, N (%)	3349 (67.0)	1584 (67.7)	1650 (67.8)	
Mean age at diagnosis, years (SD)	58 (15)	56 (17)	49 (17)	
Medications				
Methotrexate (MTX)	4167 (83.4)	1789 (76.4)	1512 (62.1)	<0.001
MTX per os	3998 (80.0)	1706 (72.9)	1406 (57.8)	
MTX s.c.	625 (12.5)	308 (13.2)	310 (12.7)	
Sulfasalazine	2520 (50.4)	1090 (46.6)	1362 (56.0)	<0.001
Hydroxychloroquine	3603 (72.1)	1357 (58.0)	866 (35.6)	<0.001
Leflunomide	256 (5.1)	121 (5.2)	119 (4.9)	0.89
Azathioprine	65 (1.3)	31 (1.3)	23 (0.9)	0.37
Aurothiomalate	42 (0.8)	12 (0.5)	8 (0.3)	0.023
Auranofin	4 (0.1)	2 (0.1)	2 (0.1)	0.99
Cyclosporine	13 (0.3)	10 (0.4)	23 (0.9)	<0.001
Prednisolone/prednisone (PRD)	3626 (72.6)	1706 (72.9)	1283 (52.7)	<0.001
Self-injected biologics (all)	131 (2.6)	125 (5.3)	76 (3.1)	<0.001
Etanercept	53 (1.1)	55 (2.4)	31 (1.3)	
Adalimumab	40 (0.8)	48 (2.1)	29 (1.2)	
Certolizumab	23 0.5)	19 (0.8)	12 (0.5)	
Golimumab	19 (0.4)	19 (0.8)	9 (0.4)	
Abatacept	8 (0.2)	5 (0.2)	1 (0.04)	
Tocilizumab	4 (0.1)	1 (0.04)	1 (0.04)	
Ustekinumab	0 (0)	0 (0)	1 (0.04)	
No anti-rheumatic medication	71 (1.4)	60 (2.6)	73 (3.0)	<0.001
Only PRD	25 (0.5)	30 (1.3)	24 (1.0)	<0.001
Number of DMARD purchases, median (IQR)	11 (7, 16)	10 (6, 14)	7 (4, 11)	<0.001

5.3.2 AxSpA patients

Of the 3577 axSpA patients, only 100 (2.8%) did not purchase any DMARDs during the first year. Some 836 (23.4%) axSpA patients initiated a self-injected bDMARD by the end of 2015 (median follow-up 3.4 years). The patients were divided into two groups according to the use of bDMARDs (A=no, B=yes) (Table 6).

In the first year after the ID, patients in group B had purchased more PRD, MTX, and other csDMARDs compared to the patients in group A; only SSZ purchases were more common in group A. Further, in group B, 58% (13.6% of all axSpA patients) started their bDMARD already within one year (Table 6).

Table 6. Baseline characteristics and the numbers and proportions of DMARD purchasers among group A and B axSpA patients during the whole first year after the ID.

	Group A	**Group B**	***p*-value**
Number of patients (N)	N=2741	N=836	
Females, N (%)	1458 (53)	412 (49)	0.048
Mean age at diagnosis,years (SD)	39 (13)	38 (11)	0.16
Medications, N (%)			
Methotrexate	820 (29.9)	450 (53.8)	<0.001
Sulfasalazine	2315 (84.5)	657 (78.6)	<0.001
Prednisolone	927 (33.8)	393 (47.0)	<0.001
Other csDMARDs	177 (6.5)	82 (9.8)	<0.001
Self-injected biologics	0 (0)	485 (58.0)	..
No anti-rheumatic medication	3.6	0.2	

5.4 Opioid purchases

The proportion of opioid purchasers among RA and UA patients and their controls during the year before and after the ID, further dividing the observation time into quarters, is shown in Figure 9. Also, this figure shows the proportion of NSAID and paracetamol purchasers. The corresponding results of axSpA patients (the whole group and groups A and B separately) are shown in Figure 10. The opioid purchases peaked during the last three-month period before the ID in all diagnosis groups. The drop in opioid purchases among patients took place rapidly after the ID where anti-rheumatic medication was presumably initiated; a similar drop did not exist in the control groups. After this drop, the frequency of opioid use levelled off and no significant decrease was further seen in any diagnosis groups during the observation time. Still, one year after the ID, the IA patients purchased more opioids than the controls. The use of NSAIDs and paracetamol was more common both in the RA and UA groups and in their population controls than the use of opioids; however, axSpA patients purchased opioids more often than paracetamol. Both NSAID and paracetamol purchases peaked among IA, but not among controls in a similar way as seen in opioids (Fig. 9 and 10).

Figure 9. The proportion (%) of opioid, NSAID, and paracetamol purchasers among patients with seropositive RA+, seronegative RA, and UA and their controls one year before and after the ID.

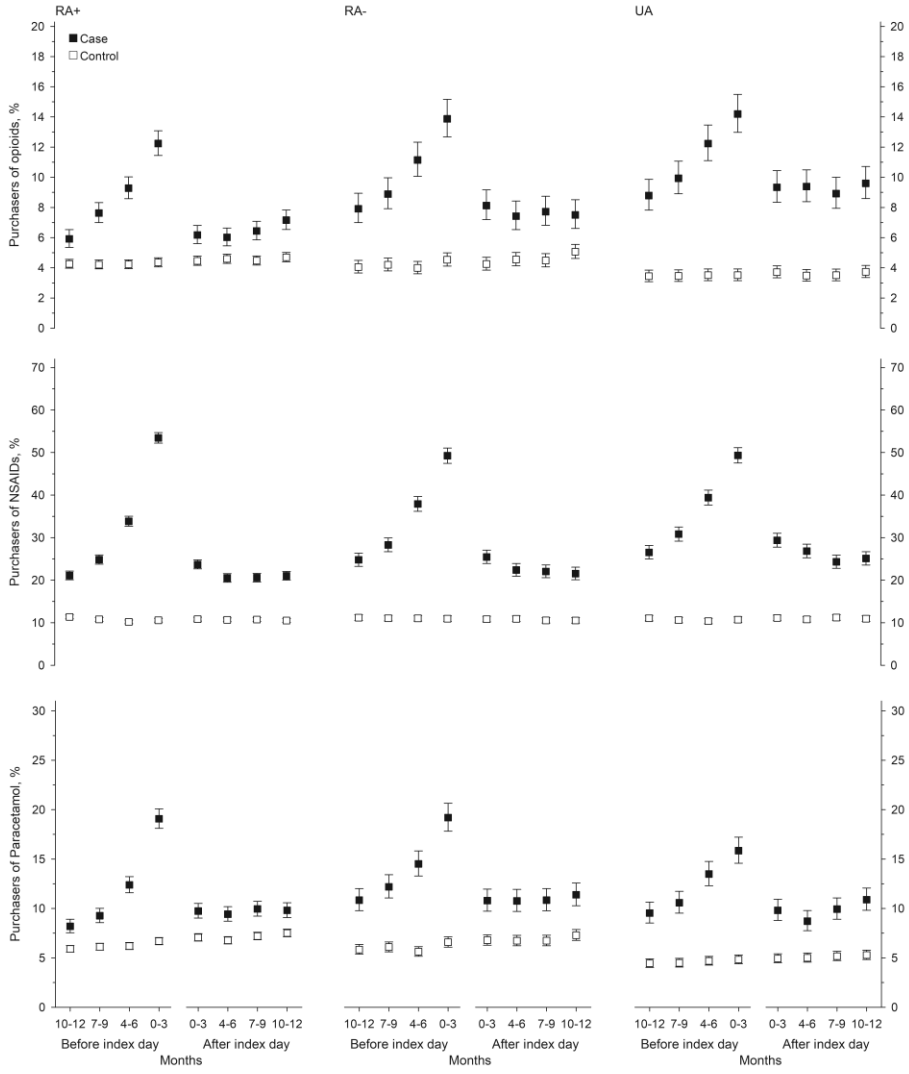


Figure 10. The proportion (%) of opioid, NSAID, and paracetamol purchasers among patients with axSpA and their controls one year before and after the ID. The results for the whole axSpA group and for groups A and B are presented separately.

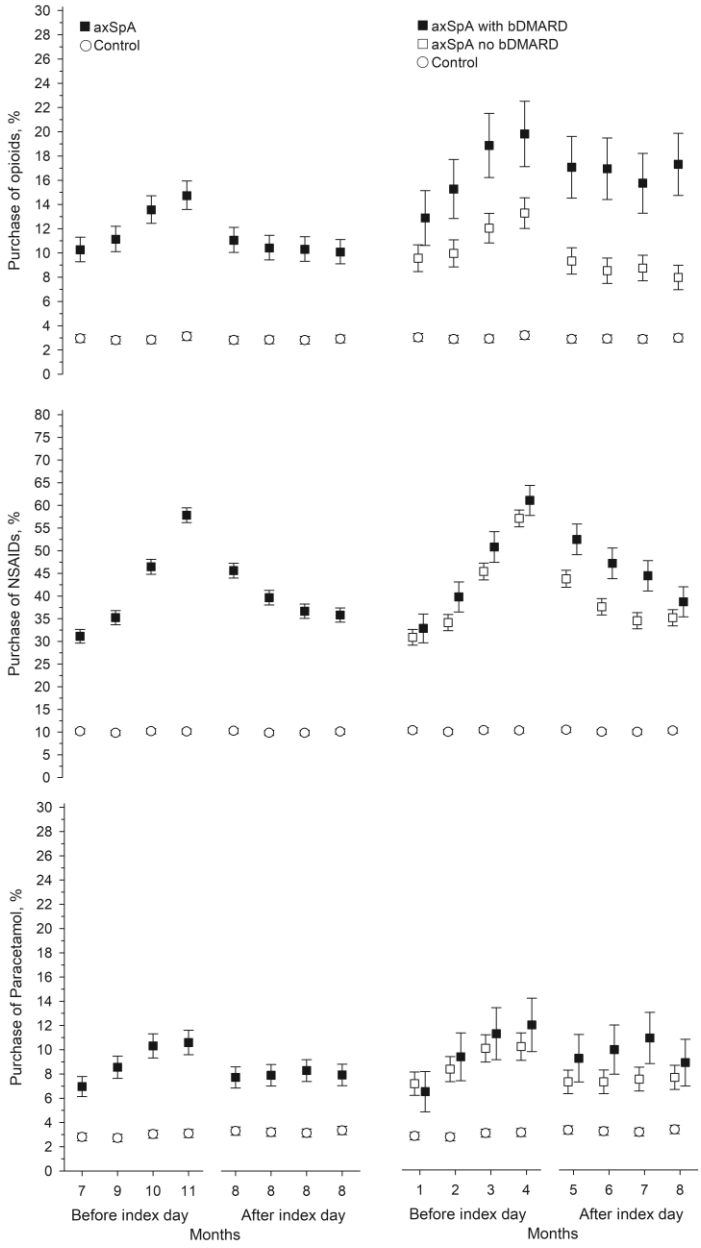


Figure 11 shows the risk ratios (RRs) of opioid purchases among RA, UA, and axSpA patients (groups A and B axSpA patients separately) one year before and after the ID by quarters compared to their controls. In RA, the RR gradually increased before the ID and was highest during the last quarter before the ID [RR 2.81 (95% CI 2.55-3.09) for seropositive RA and 3.06 (95% CI 2.68-3.49) for seronegative RA], but decreased rapidly after the ID especially in seropositive RA [RR 1.38 (95% CI 1.23-1.58)] but also in seronegative RA [1.91 (95% CI 1.63-2.24). UA patients were up to four times more likely [RR 4.04 (95% CI 3.51-4.65)] to be opioid purchasers than their controls during the last quarter before the ID, and still a 2.5-fold difference [RR 2.51 (95% CI 2.15-2.93)] remained during the whole first year after the index date. In the whole group of axSpA patients, the RR was 4.77 (95% CI 4.14-5.39) compared to the controls during the last quarter before the ID. For group A and B patients, the RRs were 4.23 (95% CI 3.63-4.84) and 6.23 (95% CI 5.23-7.41), respectively (Figure 12). During the whole year after the ID, the RRs were 2.84 (95% CI 2.59- 3.11) for all axSpA patients compared to the controls and 2.37 (95% CI 2.14-2.64) and 4.34 (95% CI 3.87-4.89) for group A and B patients, respectively. Patients in group B were 1.8 times more likely to be opioid purchasers [RR 1.82 (95% CI 1.61-2.07)] in the year after the ID than patients in group A.

Figure 11. The risk ratios of opioid purchases among patients with seropositive RA, seronegative RA, UA, and axSpA (group A and B axSpA patients separately) compared to their controls one year before and after the ID.

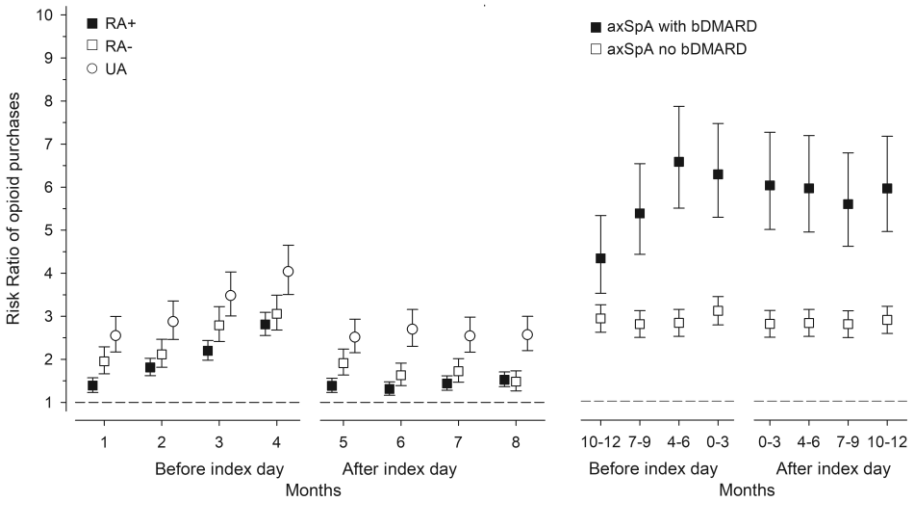


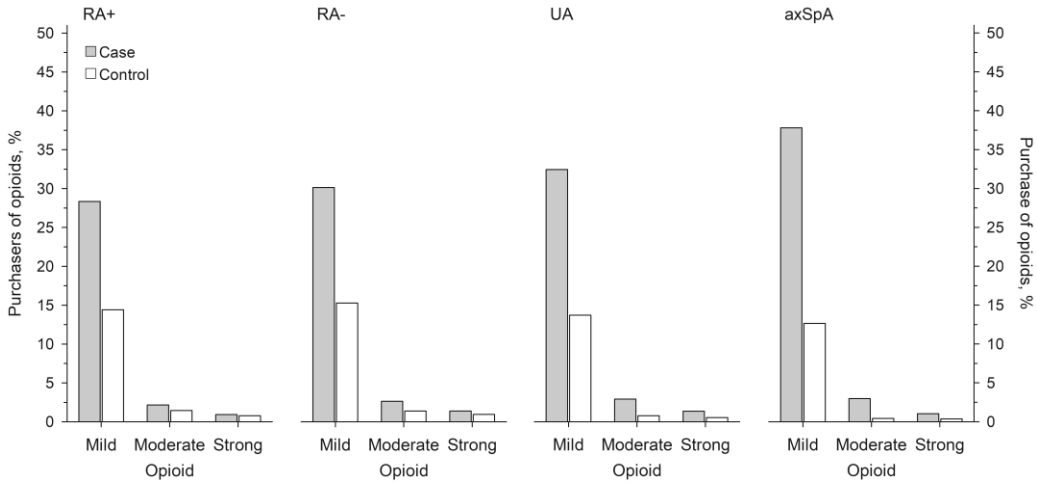
Table 7 shows the proportions of any opioid purchasers as well as long-term users (those who had at least one opioid purchase in 3/4 or 4/4 quarters within a year) during the whole year before and after the ID for each diagnosis group separately. Long-term opioid use was more common among IA patients both before and after the ID compared to their controls. After ID, UA patients appeared to be more likely (RR 3.5) long-term opioid users than RA patients (RR 1.3 and 1.9 for seropositive and seronegative RA, respectively), although they were substantially younger at diagnosis than the RA patients. Still, of all studied IA diagnoses, long-term opioid use was most common among axSpA patients (RR 6.6 after ID), who were also the youngest at diagnosis. Instead, in the control population's long-term opioid use increased with rising age. Of the group A axSpA patients, 4.8% were long-term opioid users in the year before ID and 5.0% in the year after ID, whereas in group B, the respective numbers were 8.6% and 10.5%. Based on the differences in the proportions of opioid purchasers among the cases and controls, approximately 1-4% of RA and UA patients and 5% of axSpA patients seem to use opioids long-term for their arthritis pain. The RRs did not differ significantly between the years before or after the index date in any of the three diagnosis groups, indicating that long-term opioid use may stabilize early in the disease course. Adjustment by education level did not have a major impact on the RRs for opioid use in any of the diagnosis groups; the adjusted RRs were slightly lower across the board (Table 7).

Table 7. The proportion (%, with 95% CI) of individuals that purchased opioids at least once or were long-term opioid users among patients with seropositive RA, seronegative RA, UA, and axSpA and their controls one year before and after the ID. Also, the risk ratios for any opioid purchase and long-term opioid use with 95% CIs are shown, as well as the adjustments by education level

	Case % (95% CI)	**Control** % (95% CI)	RR (95% CI) Crude	RR (95% CI) Adjusted
Any opioid purchasers				
RA+				
Before	22.7 (21.7 to 23.8)	9.8 (9.4 to 10.2)	2.32 (2.18 to 2.47)	2.27 (2.13 to 2.42)
After	15.4 (14.5 to 16.3)	10.9 (10.5 to 11.4)	1.41 (1.31 to 1.51)	1.38 (1.28 to 1.48)
RA-				
Before	25.0 (23.4 to 26.5)	10.1 (9.5 to 10.8)	2.47 (2.26 to 2.69)	2.43 (2.23 to 2.66)
After	16.4 (15.1 to 17.7)	11.3 (10.6 to 12.0)	1.45 (1.31 to 1.60)	1.42 (1.29 to 1.57)
UA				
Before	26.5 (24.9 to 28.1)	8.9 (8.3 to 9.5)	2.97 (2.72 to 3.25)	2.94 (2.68 to 3.21)
After	19.7 (18.3 to 21.2)	9.5 (8.9 to 10.2)	2.07 (1.88 to 2.28)	2.04 (1.85 to 2.24)
axSpA				
Before	29.8 (28.3 to 31.3)	8.1 (7.6 to 8.6)	3.67 (3.38 to 3.98)	3.64 (3.36 to 3.95)
After	21.7 (20.3 to 23.0)	7.8 (7.3 to 8.3)	2.78 (2.54 to 3.05)	2.76 (2.52 to 3.02)
Long-term opioid users				
RA+				
Before	3.2 (2.8 to 3.7)	2.2 (2.0 to 2.4)	1.46 (1.24 to 1.73)	1.40 (1.19 to 1.66)
After	3.3 (2.9 to 3.8)	2.5 (2.2 to 2.7)	1.34 (1.14 to 1.58)	1.29 (1.09 to 1.51)
RA-				
Before	4.7 (4.0 to 5.5)	2.0 (1.7 to 2.3)	2.33 (1.87 to 2.90)	2.26 (1.82 to 2.81)
After	4.6 (3.9 to 5.4)	2.4 (2.1 to 2.8)	1.89 (1.53 to 2.33)	1.83 (1.48 to 2.26)
UA				
Before	5.4 (4.6 to 6.3)	1.5 (1.2 to 1.7)	3.67 (2.92 to 4.61)	3.57 (2.85 to 4.49)
After	5.5 (4.7 to 6.4)	1.6 (1.3 to 1.9)	3.46 (2.77 to 4.33)	3.37 (2.70 to 4.21)
axSpA				
Before	5.7 (4.9 to 6.5)	1.0 (0.8 to 1.2)	5.43 (4.32 to 6.82)	5.34 (4.25 to 6.70)
After	6.3 (5.5 to 7.1)	1.0 (0.8 to 1.1)	6.58 (5.22 to 8.30)	6.45 (5.12 to 8.14)

The majority of purchased opioids were mild opioids in all diagnosis groups (Figure 12); they were purchased by 37.8% of axSpA patients, 32.4% of UA patients, 30.1% of seronegative RA patients, and 28.3% of seropositive RA patients at least once during the two-year observation time. IA patients purchased more opioids of any type (mild, moderate, or strong) compared to controls.

Figure 12. The distribution of opioid purchasers by the opioid type (mild, moderate, strong) among patients with seropositive RA, seronegative RA, UA, and axSpA during the two-year observation period. For each diagnosis group, the results are compared to age-, sex-, and place of residence-adjusted controls. Patients having combined use of different opioid types are shown in all groups in question



It was also evaluated whether the IA patients' age, gender, education level, and certain drug purchases were associated with opioid purchases during the year after the ID (Table 8). Gender did not play a significant role among RA or UA patients, but in axSpA, males were less likely to purchase opioids. With growing age, the likelihood of opioid purchases increased in RA and UA, but not in axSpA, where age did not affect the probability of opioid purchases. The effect of education level was analysed by using basic education (compulsory basic comprehensive school) as a reference, whereas middle-level, lower high-level, and upper high-level education were variables. In seropositive RA, UA and axSpA, a higher education level was associated with less opioid use. Further, the increasing number of PRD purchases during a year after the ID predicted greater risk for opioid use among seropositive RA, UA and axSpA patients. Those IA patients who had purchased psycholeptics (ATC code N05), psychoanaleptics (ATC code N06), or cardiovascular drugs (ATC codes C1-10) were more likely to buy opioids. (Table 8)

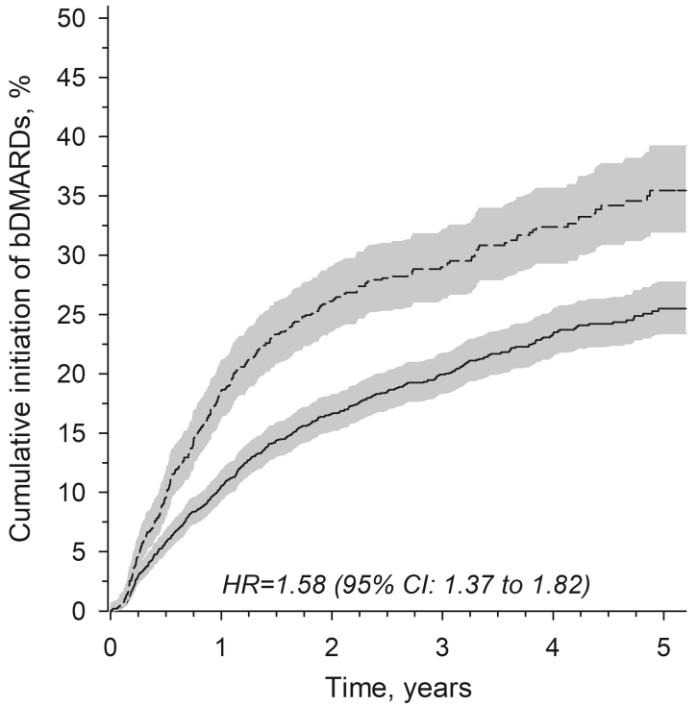
Table 8. Multivariable analysis to evaluate factors associated with opioid purchases during the year after the ID

	RA+ OR (95% CI)	P-value	RA- OR (95% CI)	P-value	UA OR (95% CI)	P-value	axSpA OR (95% CI)	P-value
Male sex	1.11 (0.95 to 1.28)	0.18	0.93 (0.75 to 1.16)	0.52	1.00 (0.81 to 1.17)	0.98	0.79 (0.67 to 0.93)	0.006
Age per 10yr	1.15 (1.09 to 1.21)	<0.001	1.11 (1.03 to 1.19)	0.005	1.10 (1.03 to 1.17)	0.003	0.97 (0.90 to 1.04)	0.36
Education level		<0.001*		0.13*		0.006*		<0.001*
basic	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
middle	0.88 (0.75 to 1.04)		1.32 (1.03 to 1.69)		1.04 (0.82 to 1.32)		0.93 (0.73 to 1.18)	
lower high	0.76 (0.61 to 0.95)		0.83 (0.61 to 1.13)		0.83 (0.63 to 1.09)		0.67 (0.51 to 0.89)	
upper high	0.55 (0.38 to 0.80)		0.74 (0.45 to 1.22)		0.57 (0.37 to 0.88)		0.52 (0.36 to 0.76)	
Number of PRD purchases		0.024*		0.74*		0.015*		<0.001*
0	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
1	1.20 (0.94 to 1.54)		1.39 (1.00 to 1.93)		1.15 (0.88 to 1.51)		1.62 (1.29 to 2.03)	
2	1.02 (0.79 to 1.32)		1.06 (0.76 to 1.50)		0.95 (0.68 to 1.32)		1.45 (1.02 to 2.08)	
3+	1.25 (1.05 to 1.49)		1.10 (0.85 to 1.42)		1.38 (1.10 to 1.74)		1.92 (1.46 to 2.54)	
Other drug purchases								
Psycholeptics	1.88 (1.57 to 2.26)	<0.001	2.19 (1.71 to 2.80)	<0.001	1.81 (1.41 to 2.32)	<0.001	2.36 (1.84 to 3.01)	<0.001
Psychoanaleptics	1.60 (1.30 to 1.96)	<0.001	2.04 (1.56 to 2.67)	<0.001	2.22 (1.73 to 2.84)	<0.001	1.85 (1.48 to 2.32)	<0.001
Cardiovascular drugs	1.50 (1.12 to 2.01)	0.006	2.08 (1.29 to 3.34)	0.002	2.04 (1.38 to 3.09)	<0.001	1.27 (0.87 to 1.84)	0.21

*P for linearity

AxSpA patients who made at least one opioid purchase in the 12 months preceding the ID were 1.58 times more likely to start a bDMARD by the end of 2015 compared to those who did not purchase any opioids before the ID (Figure 13).

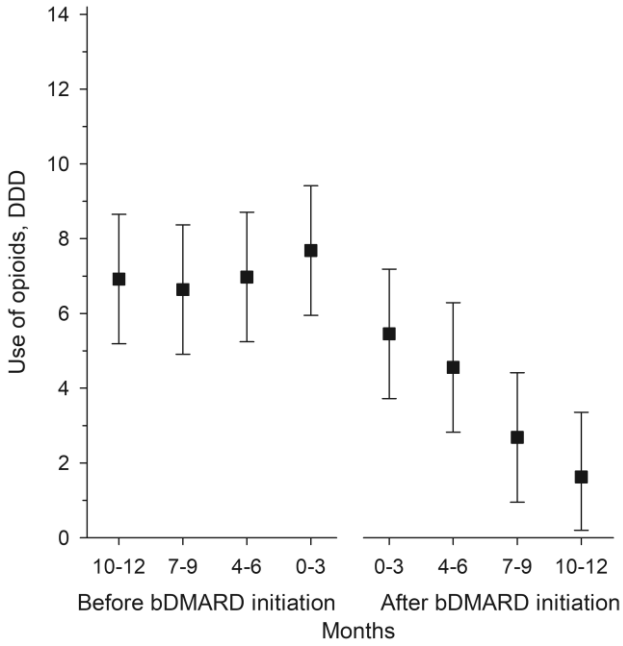
Figure 13. Cumulative rate of initiators (%) of bDMARDs by the end of 2015 among axSpA patients who had at least one opioid purchase (dotted line) or no opioid purchases (continuous line) during the year before the ID.



Of the 836 group B axSpA patients, 310 (37%) purchased opioids at least once in the year before bDMARD initiation and 245 (29%) did so in the year after bDMARD initiation, thus a small (8 percentage point) decline in the overall proportion of axSpA patients purchasing opioids following a bDMARD initiation was observed. Of those with opioid purchases before bDMARDs, 165 (53%) had at least one opioid purchase after bDMARD initiation, while 15% of the group B patients purchased opioids for the first time after the initiation of bDMARDs. On the group level, however, after the initiation of a bDMARD, a clear decline was seen

in the opioid consumption (presented as DDD per 1,000 inhabitants per three-month period) during the following year (Figure 14). The opioid consumption (DDD) was 6.9 (95% CI 5.2-8.7) during the time period of 10 to 12 months before the bDMARD initiation, which increased to 7.7 (95% CI 6.0-9.4) during the three-month period before bDMARD initiation and declined to 1.6 (95% CI 0.2-3.4) during the time period of 10 to 12 months after the bDMARD initiation. There were 412 women and 424 men in group B. During the year after bDMARD initiation, 33% (N=133) of the women and 26% (N=109) of the men purchased opioids (p=0.020).

Figure 14. The consumption of opioids by axSpA patients, presented as defined daily doses (DDDs) one year before and one year after the initiation of a biological disease-modifying drug.



6 DISCUSSION

The data presented in this register-based study brings important and novel information on the time trends in IA incidences during the first 15 years of this millennium. It also describes IA patients' early DMARD and pain medication, especially opioid use between the years 2009 and 2015. With the utilization of the unique and nationwide SII register databases, which allow the inclusion of basically all Finnish early IA patients that have started on DMARDs (a total number of almost 60,000 patients), this study provides a broad picture of the overall disease burden of IAs in Finland.

6.1 Temporal trends in the incidences of IAs

Comparing the IA incidence figures amongst various areas, countries, or time points is challenging, since the study designs and case definitions may differ between the reports. The classification criteria of a specific IA may have changed over time, and the differential diagnosis between IAs is not always upfront. Mainly, the diagnosis has been set on clinical grounds, and there are variations in the fulfilment of classification criteria. Some early IA studies reporting the total incidence of IAs have also registered patients with, e.g. viral or crystalline arthritides and are often based on population samples, of which some may be small in size or biased. This study comprised patients with a continuing IA in need of DMARD initiation, and it is the first incidence study of the total IA incidence in Finland to cover the whole population.

In Finland, the incidence rate of all IAs is 1.6 times more common among women than among men. Between 2000 and 2014, the mean annual IA incidence rate per 100,000 was 115 for women and 70 for men. Between the five-year periods 2000-2004 and 2010-2014, the age-adjusted incidence rates increased by 3% in women and by 10% in men, reaching statistical significance. Due to the increased number of people at risk, the mean yearly number of incident IA patients between the first and

the last 5-year periods grew by 12%, meaning almost 450 more diagnosed IA patients on average per year, thus increasing the burden of patients on rheumatology clinics. Between the single years 2000 and 2014, the mean yearly number of incident IA patients grew even more, by 23%. The utilized national registers comprehensively include early IA patients that are diagnosed by rheumatologists and evaluated to require DMARDs. This supports the reliability of the current results. It is unlikely that the true incidence of IAs would be lower than the current estimates, which may in fact exclude the mildest cases. The possible other reasons for the observed growth in the incidence rates can only be speculated. It is possible that the number of new true cases in some IA groups may have risen, or more of them may have visited a rheumatologist. The attention on early diagnosis and treatment may have resulted in DMARDs being prescribed for milder cases that might not have even been diagnosed in the past and consequently, more certificates have been filed and more reimbursements granted than in the past. The increased awareness of the diseases and progressed diagnostic tools can influence the observed incidences, thus both increasing and reducing the numbers. Also, the ageing of the population, especially of the baby boom generation (those born between 1946 and 1964) have probably caused a rise in the crude incidences of some IA groups. Although the IA incidence rate was clearly higher in women than in men, it increased more rapidly among men compared to women between 2000 and 2015, thus perhaps the gender gap will somewhat level off in the future.

A decrease in the mean age at diagnosis among women was found, mostly caused by the rising number of patients in those diagnosis groups that have contracted such an illness at a younger age. Due to the growing incidence of IAs, the declining age at diagnosis in some IAs, the need for life-long monitoring and treatment, and the longer overall life expectancy of the population, the burden caused by IAs on the health care system has been amplified. This burden has affected especially rheumatologic clinics, which are primarily in charge of diagnosing and treating IA patients. In Finland, it has been estimated that there will be a threatening shortage of working-aged rheumatologists in the future (Rellmann 2016), thus taking care of the demands of rheumatology care will be challenging. A study from the USA, based on emergency department visits, hospitalizations, and mean charges from visits involving arthritis and other rheumatic conditions, also discovered the total burden of IA to be increasing (Han et al. 2016).

The incidence of seropositive RA did not change significantly, while that of seronegative RA declined. Since the scoring system in the new ACR/EULAR classification criteria for RA emphasizes the significance of RF or ACPA and more joint involvement is required at diagnosis, the fulfilment of the criteria for seronegative RA is harder; thus seronegative arthritis may more frequently than before be categorized as UA or PsA. This may explain why the incidence of seronegative RA declined whereas that of UA and PsA increased in this study. Also, the rising PsA incidence may be due to the advanced education and the rheumatologists' better awareness of the typical PsA signs (e.g. family history or nail changes) (Wilson et al. 2009).

The incidence of axSpA rose in both genders during the 15-year observation period. Better diagnostic resources (e.g. the availability of MRI) have probably affected this increase. The 2009 ASAS classification criteria for axSpA has raised concerns about increasing overdiagnosis (van der Linden and Khan 2016), but as long as clinicians remember to separate classification criteria from diagnostic criteria, this should not become a problem. Nevertheless, it is most likely that in this study, the incidence of axSpA is rather underestimated than overestimated, since the early and mild cases were not included due to the methods used. The increasing proportion of women in the axSpA group noted in this study may be explained by the growing number of nr-axSpA patients, since the sex distribution is known to be more balanced in nr-axSpA compared to AS (Sieper and Poddubnyy 2017).

A receding trend in the incidence of SLE was visible, which may be explained, e.g. by a decline in real disease cases or a decline in the prescription of DMARDs (for mild cases). The increase in the use of intravenous therapies administered in the hospitals (e.g. RTX, belimumab) is a possible but unlikely explanation, since those patients have usually tried conventional therapies first and are thus found on the SR register.

The group under the ICD-10 code of M35 includes separate diagnoses ranging from SS to overlap syndromes, UCTD, and PMR. Unfortunately, it was impossible to distinguish between these specific diseases from the register data. In addition, SS patients not needing DMARDs and most PMR patients treated only with PRD are not found in the SR register. However, it was decided to keep the M35 group in the analysis since it included a rather high number of patients (regardless of the possible underestimation), who are treated with DMARDs and thus burden the health care system.

At its best, an epidemiologic incidence study could help to better understand the factors that play roles in the initiation of IAs. However, in the absence of clinical and health behaviour data, this study provides no clear explanations for these points.

6.2 DMARD use in early IA

6.2.1 RA and UA patients

DMARD treatment for early RA and UA patients was initiated actively in the current study. Within a month from the ID, over 90% of the RA patients had purchased DMARDs and close to 70% MTX. In seropositive patients, the DMARD coverage was highest, and by the end of the first year after ID, only 1.4% of the seropositive and 2.6% of the seronegative RA patients had not purchased any DMARDs. Among UA patients, the DMARD coverage was slightly less comprehensive.

In Finland, the proportion of early RA patients starting the triple combination during the first month increased between 2000 and 2007 (Rantalaiho et al. 2011), and this trend continued in this study. However, only 22% of early seropositive RA patients started the triple therapy advocated in the latest Finnish treatment guidelines (Current Care Guidelines 201). The use of triple therapy may be neglected if patients have comorbidities or polypharmacy contraindicating certain medications. Further, in the previous Finnish guidelines from 2009, the start of the triple therapy and low dose PRD was recommended only for patients with very active RA, but not routinely for all patients as the first option. Real-life patients diagnosed with RA infrequently have as active disease as patients in clinical trials (Sokka and Pincus 2003), thus rheumatologists may consider strictly following the recommendations unnecessary and base their decisions more on the T2T principle (Smolen et al. 2016b). Either way, in the absence of data on the disease activity levels, no further conclusions can be drawn on whether only one-fifth of the patients in this real life cohort had the active disease demanding triple therapy.

Although the triple therapy was not initiated according to recommendations, other MTX-based combination therapies (two DMARDs) were more common: almost half of the seropositive RA patients, 36% of seronegative RA patients, and 16% of UA patients started it within a month.

These findings may not be comparable with studies in other settings. However, studies of early RA patients from different countries have shown that it may take several months or even longer before DMARDs are initiated (Widdifield et al. 2011, de Thurah et al. 2010, Bonafede et al. 2012, Bonafede et al. 2018, Kern et al. 2018, Jamal et al. 2011, Manara et al. 2016, Kiely et al. 2009). Fortunately, there are also studies showing better DMARD coverage (Lukas et al. 2009, Tavares et al. 2011, Fakhouri et al. 2018).

In real life, implementing recommendations is often suboptimal, but eventually they do bring about improvement in the use of DMARDs (Judge et al. 2015). The Finnish treatment recommendation calls for triple therapy, which is initiated only in part of the early RA patients; however, MTX initiation seems to be quite comprehensive in Finland compared to some other countries (Lukas et al. 2009, Kiely et al. 2009, de Thurah et al. 2010, Manara et al. 2016). Thus, the strict national treatment recommendations, such as the recommendation for triple therapy initiation in early RA in Finland, will probably lead to the best outcomes.

The number of DMARD purchases during the first year after ID was two times more common among the patients initiating the FIN-RACo combination than among those patients who did not start with the FIN-RACo combination. Frequent purchases suggest regular drug usage and a good survival rate with the FIN-RACo combination.

In the treatment of early UA, EULAR recommendations favour MTX as the first drug of choice (Combe et al. 2017). No distinct Finnish treatment recommendations for UA exist. SSZ has traditionally been a common choice in seronegative oligoarthritis in Finland, especially of the large and medium-sized joints. UA patients in this study most commonly initiated either SSZ (46%) or MTX (43%), while only 16% started a combination therapy and 3% a triple therapy.

In RA, bDMARDS are used as a second-line therapy after csDMARD failure, although a few meta-analyses have shown their short-term efficacy advantages among csDMARD-naïve RA patients (Singh et al. 2017, Cai et al. 2018, Albert et al. 2015). However, long-term efficacy outcomes of initial bDMARD (TNFi) treatment are not entirely clear (Gulácsi et al. 2019). According to these results, the initiation of self-injected bDMARDs was most common (5.3%) among seronegative RA patients, but overall, the role of bDMARDs in the first-year treatment of RA and UA was small, suggesting that combination csDMARDs work effectively. The poorer treatment outcomes with csDMARDs and greater need for switching to

bDMARDs in the seronegative RA group could be explained by the heterogeneity of this group, as was shown in a recent 10-year observational study (Paalanen et al. 2019). Further, due to the latest classification criteria, the diagnosis of seronegative RA requires the involvement of at least 10 joints, corresponding to a very active disease; thus, some of the patients in this group may not respond to traditional treatments.

6.2.2 AxSpA patients

In axSpA, both the latest ACR and EULAR guidelines recommend the initiation of bDMARDs after the failure of NSAIDs in the active disease (ASDAS ≥2.1 or BASDAI ≥4, elevated CRP, and/or the presence of inflammation on MRI) (Ward et al. 2016, Ward et al. 2019, van der Heijde et al. 2017). In Finland, the SII requires documentation of the previous use of at least one csDMARD before an SR for a bDMARD can be granted (Social Insurance Institution Drug Requirements). Thus, not surprisingly, only 14% of the axSpA patients in this study initiated a self-injected bDMARD within a year of diagnosis. Compared to the other Nordic countries, the prevalent and incident bDMARD use between 2010 and 2016 was the lowest among Finnish AS patients; however, the data from Finland was obtained from the ROB-FIN register, which covers only 60% of all Finns with bDMARDs for rheumatic diseases (Glintborg et al. 2018).

Nevertheless, early bDMARD initiation after NSAID failure may not be necessary for all axSpA patients. A reasonable proportion of patients in our study seemed to manage well with SSZ; 85% of the patients in group A used SSZ, and their need for other csDMARDs and PRD as well as pain medication was lower than in group B. Of course, herein lies confounding by indication. However, a previous Finnish study showed that the majority of AS patients were able to use SSZ as a monotherapy for a long median survival time (4.5 years), indicating that SSZ may delay the need for bDMARDs by several years (Relas et al. 2014a).

The axSpA phenotype may have an impact on the drug choice, but unfortunately, the data of disease phenotypes could not be obtained from the registers. Thus, the proportions of patients with purely axial SpA, peripheral SpA, or combinations of the two were not known in this study. The rather high proportion of MTX users in group B may indicate peripheral disease, but not necessarily, since MTX is commonly combined with TNFi to prevent drug antibody formation. During the

last five years, more attention has been paid to the correct recording of ICD-10 codes in rheumatic diseases in Finland. For example, peripheral spondyloarthritis, which does not fit into any specific disease criteria, might have previously been recorded as the ICD-10 code M46, but nowadays it is more frequently recorded as M13.9 (UA). This may explain some differences in the incidences and drug usages of Finnish IA patients compared to those in other countries.

In the current study, women in group B seemed to be less responsive to bDMARDs than men, since their opioid use after bDMARD initiation was greater compared to men.

6.3 IA patients' opioid use

Previous studies have shown an elevated risk for excessive opioid use among IA patients, and this was also found among Finnish IA patients who used opioids more often than their general population comparators (studies III and IV). At least one opioid purchase was made by 23-27% of RA and UA patients during the year preceding the ID, and 15-20% of these patients made a purchase during the year following the ID. The respective numbers for axSpA patients were 30% and 22%. Conversely, approximately 8-11% of the controls used opioids. Based on the differences in the proportions between the patients and controls, 5-14% of IA patients seem to use opioids for their arthritis pain during the year after the ID. Since previous studies of IA patients' opioid use are performed in different settings and are not specifically limited to patients with recent onset disease, the current results cannot directly be compared with them. However, in the US, the reported proportions of any opioid users are 40-72% among RA patients and 22-54% among AS patients; these numbers being higher than what was found in Finland.

In the present study, opioid purchases reached the highest levels just before the ID in all diagnosis groups. Especially in seropositive RA, opioid use decreased rapidly as the diagnosis had been set, presumably indicating the initiation of anti-rheumatic medication and effective disease-control with DMARDs. Compared to RA, UA patients had a higher risk of using opioids, although they were significantly younger at diagnosis than the RA patients. Instead, opioid use in the general population became more common with a rising age. The possible reasons for this can only be speculated. Controlling arthritis pain may be more challenging in UA

than in RA, because of somewhat less aggressive DMARD initiation. Patients with seronegative RA have been shown to experience higher disease activity and delayed remission, partly due to changed diagnostics and the requirement for more joint involvement at diagnosis (Coffey et al. 2017), which may partly explain the differences in opioid use between the two RA serotypes. Furthermore, seronegative RA and UA patients may actually have another condition, such as crystal arthropathy, osteoarthrosis, or hemochromatosis, which may not respond to DMARDs; this explains why those groups had a greater need for pain medication than the seropositives.

Still, it seems that out of all IA patients, axSpA patients have the highest risk of becoming opioid users, although the mean age in this group is the lowest. This was seen especially among those axSpA patients who subsequently initiated a bDMARD. Compared to the population controls, axSpA patients were 6.6 times, UA patients 3.5 times, seronegative RA patients 1.9 times, and seropositive RA patients 1.3 times more likely to be long-term opioid users a year after the ID. A similar finding was observed in a large US study where long-term opioid use among patients with different inflammatory rheumatic diseases (RA, SLE, PsA, and AS) was most common (RR 2.73) among AS patients compared to age- and sex-matched patients with hypertension (Chen et al. 2019a).

During the year after the ID, long-term opioid use was seen in 3-6% of RA and UA patients, 11% of those axSpA patients who initiated a bDMARD during the follow-up (group B), and 5% of those axSpA patients treated only with csDMARDs (group A). Although the definition of long-term opioid use varies between the studies, the previously reported numbers from the US range from 12% to 25% in RA (Zamora–Legoff et al. 2016, Lee et al. 2018, Curtis et al. 2017, Kern et al. 2018) and from 10% to 77% in AS (Dau et al. 2018, Sloan et al. 2019, Chen et al. 2019a), and are thus higher than the current results.

The differences in IA patients' long-term opioid use frequencies between the years before and after the ID did not reach statistical significance in any of the diagnosis groups, thus these results suggest that those who end up being long-term users will continue to use opioids chronically still after DMARD initiation, and they are consequently at risk for opioid addiction. Likewise, patients with osteoarthritis who undergo joint replacement surgery, and thus should be pain free after some time postoperatively, are at risk of prolonged opioid use at least one year after surgery if they have used opioids preoperatively (Franklin et al. 2010). Even if opioids are

initially prescribed for short-term pain, there is always a risk for opioid dependence, as has been shown among emergency department patients (Hoppe et al. 2015). Once started, the threshold for renewing opioid prescriptions may be lower. Thus, harmful long-term use of opioids may be a result of painful comorbidities, contraindications for NSAIDs, wrong diagnoses, or too liberal prescription habits by physicians.

AxSpA patients' opioid consumption by dose (in DDDs) started to decline gradually once a bDMARD was initiated, and the trend was still declining at one year of bDMARD use. Recently presented but not yet published results from Iceland, however, showed that after the initiation of the first-line TNFi, IA (RA, axSpA, PsA, or UA) patients' opioid consumption by dose [presented as morphine equivalent doses (MEDs)] did not decrease at the group level during two years of follow-up (Palsson et al. 2020).

In the present study, higher education level was associated with less opioid use in most IA diagnoses. Further, continuous oral GC use was a predictor of increased opioid use. Those IA patients using medications used to treat psychiatric or cardiovascular comorbidities were at a greater risk of being opioid users.

Since patients who receive an IA diagnosis and are started on DMARDs are usually monitored in rheumatologic clinics at least the first two years after diagnosis, they most likely get their drug (including opioid) prescriptions from there. Instead, the population controls as well as patients before IA diagnosis usually receive their drug prescriptions from primary care physicians. Thus, this study probably describes the physicians' prescription patterns even more than their patients' opioid need. A drop in opioid use was found after the ID when patients were presumably monitored by the rheumatologists, but the numbers did not reach population levels during the follow-up. Previous studies have shown that almost half of the RA patients using opioids receive their opioid prescriptions from a rheumatologist (Curtis et al. 2017), and the physician's opioid prescription habits greatly affect the RA patient's risk of later becoming a long-term opioid user (Lee et al. 2020). Thus, it is important that rheumatologists, especially in the early disease, carefully check the diagnostics and weigh up the treatment options before they renew the opioid prescription.

In all diagnoses, the purchases of NSAIDs and paracetamol showed similar trends as opioids (a peak before diagnosis and a reduction after that), even though the percentages of patients purchasing these medications were markedly higher, except in the axSpA group, in which both NSAIDs and opioids were purchased more often than paracetamol.

6.4 Strengths and limitations

The main strengths of the register-based substudies included in this thesis were the nationwide scope and the availability of high-quality public registers. These registers offer opportunities for first-class analyses, e.g. of the incidence of IAs and the drugs purchased by IA patients. The observation periods were long, especially in study I, lasting up to 15 years. The patient identification was based on diagnoses (ICD-10 codes) formulated by qualified specialists or special clinics. Thus, the diagnoses are assumed to be reliable. Since there are clear economic benefits for the patient, practically all Finnish patients with anti-rheumatic medication for chronic IAs are entitled to reimbursement. Therefore, this cohort includes basically all those Finnish early IA patients who had been inspected and diagnosed by rheumatologists and prescribed DMARDs and GCs.

The inclusion of population controls in Studies III and IV strengthened these studies and allowed the estimation of the proportions of opioid users for the pain caused by IA itself, although the detailed indications of analgesic therapy could not be obtained from the SII's drug purchase register. In Finland, DMARDs and opioids are only available with prescriptions, thus they are inclusively covered in the utilized register.

The limitation of using register-based data is that the data are usually collected for administrative purposes and not all the information needed for research is available. A major limitation is the lack of clinical and health behaviour data. The information on disease activities and severities, exact disease phenotypes, patient-level pain scores, and smoking, among other things, would have been of great interest. Patients with a mild disease and not requiring DMARDs, e.g. patients on solely non-pharmacologic therapies or NSAIDs, are not comprehensively found in the SII's registers. Therefore, we may miss patients that the physician intends not to treat with DMARDs.

The proportion of UA patients that received a more specific diagnosis later was not known (Studies I-III). Also, some of the UA patients in this study may not be directly comparable to patients in so-called early arthritis clinics.

Since the duration of symptoms before the diagnosis was not known, it is possible that some patients were diagnosed with a time lag; thus in these cases, the DMARDs used represent the patients' initial treatment rather than the treatment of early IA (Studies II and IV). We do not know confidently whether the patients or general

population used their purchased medications as prescribed and thus the level of drug compliance. Further, the case identification (based on SRs) may partly explain the comprehensive DMARD coverage in study II.

In study I of the total incidence of IAs, IBD-associated arthritis was not analysed. The majority of the incident patients already had an SR for DMARDs on the grounds of their colitis. In addition, due to the low number of some rare rheumatic diseases such as myositis, scleroderma, and vasculitides, these diagnoses were not included in the current incidence analyses. Further, the diagnosis group M35 was heterogeneous and incidences of specific diseases within this group could not be analysed.

Both NSAIDs and paracetamol can be purchased with a physician's prescription but also over-the-counter without reimbursement, when they are not covered in the SII's Drug Purchase Register. However, the underestimation of NSAID and paracetamol consumption in the current study is likely to be equal for both patient and control groups, and thus it does not cause a substantial bias. The drugs used during possible hospital stays could not be recorded, but in Finland IA treatment is basically outpatient-based, so this should not cause too large a bias.

In study IV, the DDD was used to estimate the IA patients' opioid consumption. However, since DDDs are based on the formal indications of the WHO, there are challenges in using them in this purpose. DDD may, e.g. underestimate the true utilization of strong opioids because their DDDs are based on doses used for cancer pain. Also, opioids are not necessarily intended for everyday use, and the doses are often titrated to response, so there may be a discrepancy between the DDD and the actual daily dose (Nielsen et al. 2017).

The data on intravenously administered bDMARDs were lacking (Studies II and IV), since infusion-based drugs, like IFX or RTX, are funded by the individual hospital and are not under the reimbursement system. However, only a small proportion of patients initiate them during the first year after the diagnosis, the time period of interest in our study. According to the Finnish ROB-FIN register data (which covers approximately 60% of all Finns with bDMARDs for rheumatic diseases), the first TNF inhibitors were initiated for RA patients after a median (IQR) of 8.2 (2.4-17) years of disease duration in 2004-2014, most often with adalimumab (39%) or etanercept (39%), while IFX was a rarer choice (12%) (Aaltonen et al. 2017). The more recent ROB-FIN register data from 2010-2015 shows that the use of IFX as the first biologic in RA had decreased from 7.5% to 4.2% (Kalle Aaltonen, personal communication). RTX was the first choice for as many as 20-23% of the

RA patients. Still, the majority started self-injected drugs, and the median (IQR) point of starting the first biologic was after 10 (4.4-18) years of disease duration. Between 2010 and 2014, of the established axSpA patients with bDMARDs, 80% used self-injected bDMARDs and 20% used IFX (Nordström personal communication). Thus, even though infusion-based drugs were included in Studies II and IV, the results of the first-year treatment would not have changed markedly.

7 CONCLUSIONS

The main findings of this study are summarized as follows:

1. In 2000-2014, the overall mean annual incidence rate of IAs was 115/100,000 among women and 70/100,000 among men, and it increased slightly but significantly in both genders. At the same time, the mean age at diagnosis of some IAs decreased. As a consequence, the health care system and society will probably face a growing burden caused by factors like the rising number of patients in need of long-term monitoring in rheumatologic clinics and the use of costly medicines (study I).

2. The rheumatologist-based treatment received by the Finnish new-onset RA and UA patients between 2011 and 2015 was the early initiation of cDMARDs, mainly MTX, and often in combinations (study II). Less than 14% of the axSpA patients initiated a bDMARD during the one-year follow-up between 2010 and 2015 (study IV).

3. The proportions of opioid users among Finnish RA, UA, and axSpA patients during the first year after the diagnosis was in the range of 15-22% compared to 8-11% among their matched population controls between 2010 and 2015. Based on the differences in these proportions, 5-14% of the patients seem to use opioids for their arthritis pain, which is less than previously estimated in some other Western countries. The opioid usage among Finnish IA patients concentrated on mild agents (studies III and IV). AxSpA patients who subsequently initiated the use of a bDMARD were at the greatest risk of using opioids. However, initiation of a bDMARD seemed to decrease opioid consumption by dose during the one-year follow-up (study IV).

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10 PUBLICATIONS

PUBLICATION I

Increasing incidence and shifting profile of idiopathic inflammatory rheumatic diseases in adults during this millennium

Muilu P, Rantalaiho V, Kautiainen H, Virta LJ, Eriksson JG, Puolakka K

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Increasing Incidence and Shifting Profile of Idiopathic Inflammatory Rheumatic Diseases in Adults during this Millennium

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Keywords: Epidemiology, Rheumatoid arthritis, Ankylosing spondylitis, Spondyloarthritis, Psoriatic arthritis, Unspecified arthritis

Abstract

Objectives: To explore the trends in the incidence of idiopathic inflammatory rheumatic diseases (IIRDs) after the turn of the millennium. **Methods:** From a nationwide register maintained by the Social Insurance Institution of Finland we collected all adult patients with IIRDs granted a new special reimbursement for anti-rheumatic drugs between 2000-14. Temporal trends in the incidences of various IIRDs were estimated in three 5-year intervals. **Results:** A total of 58 405 adult patients were identified. Between 2000-04 and 2010-14, the age-adjusted incidence rate of IIRDs increased from 114 to 116/100 000 [incidence rate ratio (IRR) 1.03 (95 % CI 1.01 to 1.06)] in women and from 67 to 69/100 000 [IRR 1.10 (95 % CI 1.06-1.14)] in men. The incidence of seropositive rheumatoid arthritis (RA) remained stable while that of seronegative RA decreased. For other diagnoses, the incidences either increased (unspecified arthritis, psoriatic arthritis, spondyloarthritis), remained stable (reactive arthritis), or decreased (SLE and the group of diseases with the ICD-10 code M35). The gender difference in spondyloarthritis levelled as the incidence in women increased at a higher rate than in men. Mean age at IIRD diagnosis decreased among women. **Conclusions:** The total age-adjusted incidence of IIRDs has gradually increased, due to the increase in unspecified arthritis, psoriatic arthritis, and spondyloarthritis. This, in addition to the ascending number of individuals at risk in the population, translates into a growing burden to the health care system.

Introduction

Idiopathic inflammatory rheumatic disease (IIRD) refers to a group of disorders including rheumatoid arthritis (RA) (seropositive and -negative), juvenile arthritis, spondyloarthritis [SpA, including ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)], psoriatic arthritis (PsA), reactive arthritis (ReA), inflammatory bowel disease (IBD) -associated arthritis, systemic connective tissue disorders [systemic lupus erythematosus (SLE), Sjögren's syndrome etc], and unspecified arthritis (UA). The pathogenetic mechanisms underlying these diseases are not fully understood but both genetic predisposition and unknown environmental triggers are of importance. Studying any trends in the incidences of separate IIRDs is of great interest and can even give rise to new hypotheses on the underlying factors.

Most incidence studies focus on RA, the most common IIRD worldwide. Reports show high RA incidence rates in the northern hemisphere: Canada (54/100 000), USA (41/100 000), and Sweden (41/100 000) [1-3]; but somewhat lower in the Mediterranean region such as in Spain (20/100 000) and in the southern hemisphere like in Argentina (19/100 000) [4, 5]. Previous studies from Finland have reported varying incidence rates: a study based on a population of 1 million adults, estimated an overall RA incidence of 29/100 000 (37 among women and 21/100 000 among men) in the year 2000 [6]. In another study, the respective numbers were 44/100 000 (59 and 30/100 000) between 2000 and 2007 [7].

The current classification criteria for SpA, including both AS and nr-axSpA, have promoted early diagnosis, however, previous incidence studies mainly encompass only AS. Spondyloarthritis are in general more common in regions with a high frequency of human leucocyte antigen (HLA) B27. In Finland the incidence of AS has been reported to lie around 7/100 000 [8-10]. Worldwide, the incidences of AS range from 0.5 (Japan) to 15/100 000 (USA) [11-13].

For some reasons, the incidence of PsA has varied even more worldwide, from 0.1 to 41/100 000, in studies from Japan, Norway, Argentina, and Sweden [11, 14-16]. The estimates from Finland have ranged from 6 to 23/100 000 [8, 9, 17]. ReA is mostly self-limiting, and may stay undiagnosed, complicating the estimation of incidence. The reported rates lie between 0.6 to 9/100 000 [8, 9, 18, 19].

UA is an inflammatory arthritis which does not fit into any diagnostic category, but may later evolve into a more specific established disease. Incidence rates around 40/100 000 have been reported from Finland and Sweden [8, 16].

The incidences of SLE (2 to 7/100 000) (22-25) and Sjögren's syndrome (6 to 12/100 000) [23, 24] vary markedly worldwide. The incidence of polymyalgia rheumatica (PMR) is even more difficult to study, since it is often treated by general practitioners. The disease is among the most common IIRDs; in a population-based US study the incidence was 64/100 000 [25].

As the literature demonstrates, comparing the incidences of various IIRDs from epidemiological studies is challenging, since the case definitions may differ between studies. Mostly, patients have been diagnosed on clinical grounds, and the fulfillment of classification criteria varies. Examining the whole population is the gold standard, but seldom possible, since national registers exist only in a few countries [26].

Differential diagnosis between IIRDs is not always straightforward, and classification criteria have changed over time. True biological variation may also occur. In this report we studied all IIRDs side by side to disclose any mutual trends in the occurrence.

Methods

The Finnish social security system is organized by the Social Insurance Institution (SII) and provides all permanent residents in Finland a variety of benefits. The SII refunds (basic refund 35-50%) costs of drugs prescribed by a doctor. Patients with long-term IIRDs can be granted a special reimbursement (65-72 %) for disease-modifying anti-rheumatic drugs (DMARDs, conventional and biologic) and glucocorticoids after filing a medical certificate to SII. This certificate must describe the diagnostic procedures and prescribed medication and be written in a rheumatology clinic. SII maintains a register on the reimbursements including patients' age, sex, ICD10 code of the illness, and date of entitlement. The day of the first reimbursement decision was defined as the index date in this study.

From this national register data, we collected all patients (aged ≥18 years) granted the first special reimbursement for medications of various IIRDs from January 1st 2000 to December 31st 2014.

The patients with IIRDs were classified according to the ICD-10 code into eight groups: seropositive RA (M05), seronegative RA (M06), UA (M13), SpA including AS and nr-axSpA (M45-46), PsA (L40.5), ReA (M02), SLE (M32), and a group of diseases under the code of M35 including Sjögren's syndrome, unclassified collagenosis and PMR.

Incidence of inflammatory bowel disease (IBD) associated arthritis could not be analyzed from the register since the great majority of the incident patients already had special reimbursement for DMARDs on the grounds of their colitis. The number of patients with myositis, scleroderma, or vasculitides was low, and these diagnoses were not included in our analyses.

Statistical methods

The mean annual incidence rates per 100 000 person years in 5-year calendar time intervals (2000-2004, 2005-2009, and 2010-2014) were calculated for both sexes by dividing the number of newly diagnosed IIRD cases by the total number of population (≥18 years of age) between 2000 and 2014. Patients and the population at risk were stratified by gender and age (18-24, 25-29…90+), and crude and direct adjusted incidence rates with 95% confidence intervals (CI) were calculated assuming a Poisson distribution. Standardized incidence rate ratios (IRRs) were calculated by using Poisson or negative binomial regression models when appropriate. The patient's age and the calendar year of index date were included in the models as covariates. The assumption of overdispersion in Poisson model was tested using Lagrange multiplier test. Statistical significance for the hypothesis of linearity across categories of calendar years (2000-04, 2005-09 and 2010-14) and patients' age were evaluated by using the analysis of variance with an orthogonal polynomial contrast. Population sizes according gender and age for the calculation of incidence rates were obtained from Statistics Finland. Stata 14.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.

Ethical considerations

Permission to use databases was obtained from the SII. By the Finnish legislation, no approval of ethical committee nor patient's informed consent is required for register-based studies done without contacting study subjects.

Results

During the 15-year study period, altogether 58 405 patients (63.7 % female) contracted a new IIRD requiring the use of DMARDs. Mean age (SD) at the index date was 52 (16) years, range 18 to 96 years. Among women, the age-adjusted mean annual incidence rate of IIRDs increased from 114 [95 % confidence interval (CI) 113 to 118] to 116/100 000 (95 % CI 115 to 120) from 2000-2004 to 2010-2014 with the incidence rate ratio (IRR) of 1.03 (95 % CI 1.01 to 1.06; p= 0.008) (Fig. 1). Among men, the respective increase was from 69 (95 % CI 67 to 72) to 71/100 000 (95 % CI 69 to 74, and the IRR was 1.10 (95 % CI 1.06 to 1.14; p<0.001). Due to the increased number of people at risk, the mean yearly number of incident patients with IIRD grew 12 %, from 3696 to 4141 between the first and the last 5-year period (Fig. 1). The distribution of different IIRDs at 2014 is shown in Figure 2. The annual crude incidence rates and mean ages at the index date for each diagnosis are presented in table 1. Also, the statistical significances of linearity for age- and gender-adjusted incidences and mean ages are shown in this table.

The incidences of seropositive RA and ReA did not change significantly (table 1, fig. 3). The increase in the incidence was observed for UA, SpA, and PsA, whereas seronegative RA, group of diseases under the ICD10 code M35, and SLE showed a declining trend. The gender difference in SpA levelled as the incidence in women increased at a higher rate than in men.

The mean age at diagnosis rose significantly in seropositive and seronegative RA and PsA, and decreased in ReA and M35. No significant changes in the mean ages were detected in UA, SpA, or SLE (table 1).

As seen from figure 4A, the mean age of the Finnish population has increased during this millennium (data derived from Statistics Finland), whereas the mean age at diagnosis of IIRDs has slightly decreased, mostly among women. The age distribution of all patients entitled to a special reimbursement for anti-rheumatic medication as well as the age structure of the general population

(according to Statistics Finland) in 2014 are presented in Figure 4B.

Figure 1. **a)** Mean annual number of incident patients with idiopathic inflammatory rheumatic disease (IIRD) by sex and 5-year intervals during 2000-14 in Finland. **b)** Age-adjusted annual incidence rates of IIRDs by sex and 5-year intervals during 2000-14 in Finland.

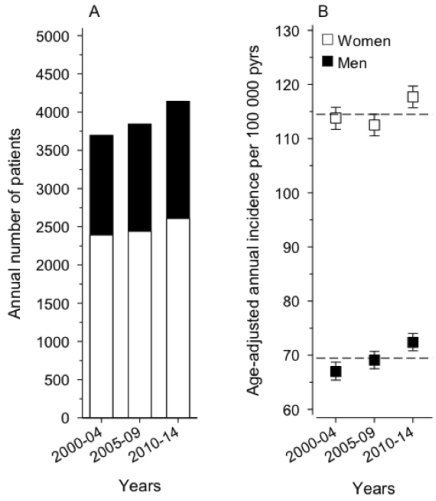

Figure 2. Number of incident idiopathic inflammatory rheumatic disease cases in Finland in 2014 [seropositive rheumatoid arthritis (RA+), seronegative RA (RA-), unspecified arthritis (UA), spondyloarthritis (SpA), psoriatic arthritis (PsA), reactive arthritis (ReA), systemic lupus erythematosus (SLE), and a group of diseases under the ICD10 code M35].

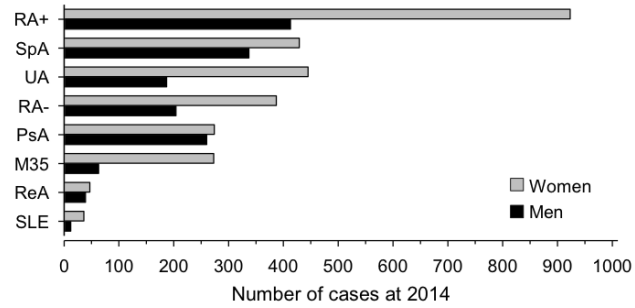

Figure 3. Age-adjusted annual incidence rates by sex for seropositive rheumatoid arthritis (RA+), seronegative RA (RA-), unspecified arthritis (UA), spondyloarthritis (SpA), psoriatic arthritis (PsA), reactive arthritis (ReA), systemic lupus erythematosus (SLE), and a group of diseases under the ICD10 code M35 presented in 5-year intervals during 2000-14 in Finland.

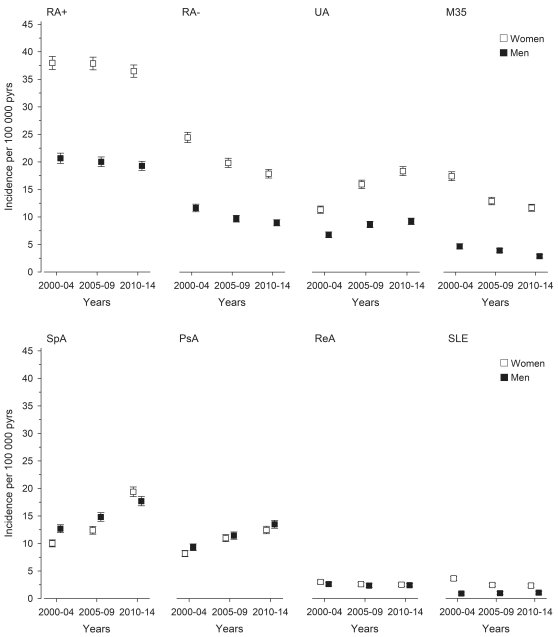

Figure 4. **a)** Age at diagnosis of an idiopathic inflammatory rheumatic disease (IIRD) and the mean age of adult population during 2000-14 in Finland. White dots refer to the age of women and black dots to the age of men at time of IIRD diagnosis. White squares refer to the mean age of general adult female population and black squares to the mean age of adult male population. **b)** Age and gender distribution of incident Finnish patients awarded a special reimbursement for anti-rheumatic medication in 2014. The black lines are indicating the age structure of general population.

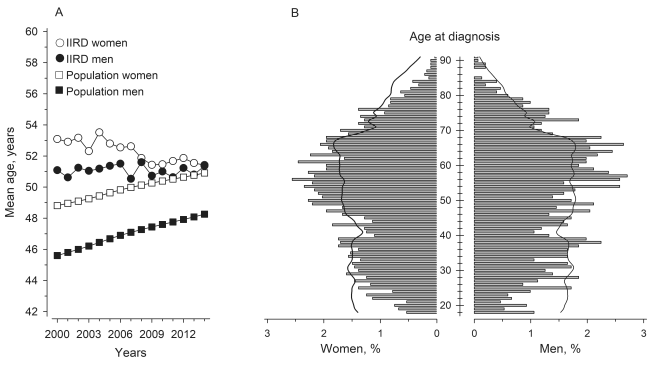

Table 1. Total number of incident cases (N), mean annual crude incidence rates per 100 000, and mean ages at diagnosis for various inflammatory rheumatic diseases [seropositive rheumatoid arthritis (RA+), seronegative rheumatoid arthritis (RA-), unspecified arthritis (UA), spondyloarthritis (SpA), psoriatic arthritis (PsA), reactive arthritis (ReA), a group of diseases under the ICD code M35, and systemic lupus erythematosus (SLE)] in Finland during 2000-14.

		Incidence per 100,000				Mean age at diagnosis (SD)			
	N	**2000-04**	**2005-09**	**2010-14**	***P* for linearity**	**2000-04**	**2005-09**	**2010-14**	***P* for linearity**
RA+	18,163	29	30	29	0.055	57 (14)	57 (14)	58 (15)	<0.001
Women	12,159	37	38	37		56 (15)	57 (15)	57 (15)	
Men	6004	20	21	20		58 (13)	59 (13)	60 (13)	
RA-	9784	18	15	14	<0.001	54 (16)	55 (16)	57 (17)	<0.001
Women	6713	24	20	18		54 (16)	55 (16)	56 (17)	
Men	3071	11	10	9		55 (15)	57 (16)	59 (15)	
UA	7399	9	12	14	<0.001	48 (15)	49 (16)	49 (17)	0.12
Women	4896	12	16	18		48 (15)	48 (16)	48 (17)	
Men	2503	7	9	9		49 (15)	50 (15)	51 (16)	
axSpA	8396	12	14	18	<0.001	39 (12)	38 (12)	38 (12)	0.74
Women	4047	11	12	19		39 (12)	39 (12)	39 (12)	
Men	4349	13	15	17		38 (12)	37 (12)	38 (12)	
PsA	6702	9	11	13	<0.001	48 (13)	49 (12)	49 (13)	0.021
Women	3278	8	11	12		48 (13)	49 (13)	49 (13)	
Men	3424	9	12	13		47 (12)	49 (12)	48 (13)	
ReA	1434	3	2	2	0.063	44 (14)	42 (14)	42 (14)	0.028
Women	765	3	3	3		44 (14)	42 (14)	42 (14)	
Men	669	3	2	2		43 (13)	43 (14)	42 (15)	
M35	5535	11	9	8	<0.001	61 (16)	59 (16)	58 (16)	<0.001
Women	4504	17	13	12		60 (16)	58 (16)	57 (16)	
Men	1031	4	4	3		64 (15)	62 (14)	63 (14)	
SLE	992	3	2	2	<0.001	46 (16)	46 (16)	45 (16)	0.26
Women	833	4	2	2		46 (16)	46 (16)	45 (16)	
Men	159	1	1	1		52 (15)	47 (16)	48 (17)	

Discussion

Our study shows that the age-adjusted incidence of IIRDs has increased by 10 % in men and by 3 % in women between 2000-2004 and 2010-2014 in Finland. This increase may be attributed to many possible factors. First, the number of new biologic disease cases may have risen. Second, the number of real cases has not grown but more of them may have visited a rheumatologist. Third, the diagnostic threshold may have become lower, or DMARDs have been prescribed for milder cases and consequently more certificates have been filed and more reimbursements granted. In this study, the case identification was based on special reimbursements.

We observed that the mean age at diagnosis declined among women, mostly due to the ascending number of patients in those diagnosis groups that are contracted at a younger age. Taken together, the increasing incidence of IIRDs, younger age at diagnosis in some IIRDs, the need for lifelong monitoring and the lack of cure of IIRDs, as well as longer overall life expectancy, the burden caused by IIRDs on the health care system has increased. Especially rheumatologic clinics, that are primarily in charge of diagnosing and treating IIRD patients, face the increased burden. A study from Nebraska, USA, based on emergency department visits, hospitalizations, and mean charges from visits involving arthritis and other rheumatic conditions also found the total burden of inflammatory arthritis to be increasing [28].

In this study, seven most common phenotypes of IIRD were assessed, and in addition the cases which remained unspecific. Our study included patients with a continuing IIRD requiring anti-rheumatic medication, whereas some early arthritis studies have also enrolled patients with e.g. viral and crystalline arthritides and are often based on population samples, some of which may be small or biased [8, 9, 16, 27, 28]. Comparing the total incidence of inflammatory arthritis between different

studies is thus challenging. There are few previous estimates from Finland: A study from the Northern Savo area with the population of 206,441 identified 292 adult arthritis cases and estimated the overall incidence to be 142/100 000 in 2010 [9]. Based upon other earlier estimates from Finland, the Kuopio Arthritis Survey in 2000 and the Heinola Town Case-finding study in 1974 the incidence were 271 and 218/100 000, respectively [8, 29]. Our study is the first in Finland to cover the whole population, and we find it to be the most reliable, especially in the case of RA.

Several reports from different countries have informed about declines in RA incidence especially during the late 20th century [6, 30, 31], but also after the turn of the millennium [32]. However, some studies indicate a rising trend [2, 33]. None of the studies gave clear explanations for these trends reported but environmental factors were speculated to play possible roles. In a Finnish study using the same method as the present study, the incidence of seropositive RA was stable, while that of seronegative RA decreased between 2000-2007 [7]; similar trends continued in our study with a longer observation period.

During the past decades, several criteria have been published for classification of RA patients and they also have impact on the diagnostic working. The new ACR/EULAR classification criteria for RA, which are better at identifying early RA than the previous 1987 ACR criteria, were formulated in 2010 [34]. The scoring system in the new RA criteria emphasizes the significance of rheumatoid factor or anti-CCP antibodies. Seronegative arthritis may more often than before be categorized as unspecified (UA) or PsA. In our study, the incidence of seronegative RA decreased whereas that of UA and PsA increased linearly. One explanation for the increasing PsA incidence could be advanced education and knowledge of the rheumatologists, and who are therefore more prone to notice e.g. family history or nail changes typical to PsA. A study from the USA also showed a rising trend in the incidence of PsA during 1970-1999, and the speculated explanation was either a true change in the incidence, or a better physician's awareness of PsA, or both [35].

The incidence of SpA rose in both sexes. This is probably due to increasingly better diagnostic resources. The diagnosis has earlier depended on the presence of plain radiographic changes (sacroilitis), while nowadays the diagnosis is often supported by abnormalities in MRI, which appear earlier, but their interpretation requires expertise. However, according to the Assessment of SpondyloArthritis International Society (ASAS) classification criteria in 2009, the diagnosis of SpA does not necessarily require any radiographic changes if other findings (HLAB27 and at least two clinical features typical to SpA) are found in a patient (≥ 3 months) back pain, onset of symptoms before the age of 45. These criteria have raised concern about leading to overdiagnosis [36] but as long as clinicians are aware that classification criteria are not the same as diagnostic criteria, this should not be a problem. Either way, our figure of the incidence of SpA is a severe underestimate since patients with early and mild cases of SpA treated with non-steroidal anti-inflammatory drugs (NSAIDs) were not included, because only patients prescribed a synthetic or biologic anti-rheumatic drug are entitled to special reimbursement and registered by the SII.

AS has been reported to be more common in men, whereas the sex distribution in nr-axSpA is more balanced [37]. Thus, the increasing proportion of women in SpA group noted in our study may be explained by the rising amount of nr-axSpA patients. Somewhat similar results were reported from a retrospective, population-based study in North America including almost 25 000 patients with AS from 1995 to 2010: the incidence and prevalence of AS increased at higher rates in women than in men since the year 2003 [13].

Previous studies have shown both rising [38] or stable [21] trends in the incidence of SLE. We noticed a receding trend. This could be e.g. due to a decline in real disease cases, due to a decline in prescription of antirheumatic drugs, or due to an increase in the use of intravenously in-hospital administered therapies (e.g. rituximab, belimumab). However, the methods used in our study and the lack of clinical data provides no possibilities to draw conclusions on this.

The group under the ICD-10 code of M35 is somewhat difficult to define. The diagnoses range from Sjögren's syndrome to overlap syndromes, unclassified collagenoses, and PMR, but we have no data about these specific diseases. Further, patients with Sjögren's syndrome not needing anti-rheumatic medication and most PMR patients treated only with inexpensive prednisolone are not found in the special reimbursement register. Regardless of the possible underestimation, the number of patients in M35 group is notable, and all the patients represent those treated by DMARDs thus burdening the health care system, so we decided not to exclude the group from our analysis.

The mean age at diagnosis of an IIRD is related to the diagnosis; in general, patients with SpA are the youngest and RA patients the oldest at the onset of the disease. Previous Finnish studies have reported very similar mean ages at IIRD diagnosis compared to our results [8, 9]. Between 1975-1995, a rise in the mean age at diagnosis of RA from 50 to 59 years was observed in Finland [39].

The main strength of our register-based study is the nationwide scope with a 15-year observation period. The patient identification was based on diagnoses (ICD-10 codes) formulated by qualified specialists or special clinics. Thus, we assume the diagnoses reliable but we have no data on the fulfillment of any classification criteria. Finland belongs to those few countries that are fortunate enough to benefit from high quality public registries that offer opportunities to first class analyses of the incidence of IIRDs.

Some limitations of the present study must be kept in mind. Patients with a mild disease and not requiring DMARD's are not found in the reimbursement register. For example, part of the patients with SpA respond satisfactorily to non-steroidal anti-inflammatory drugs. Further if the disease course is short and self-limiting, like in most cases of ReA, any DMARDs will not be introduced. In addition, we did not include patients with IBD-associated arthritis and some rare rheumatic diseases. Also, the diagnosis group M35 is heterogeneous and incidences of specific diseases could not be analyzed.

At its best, an epidemiologic register study can help to better understand the factors that contribute to the initiation of rheumatic diseases. However, we lack clinical and health behavior data. Smoking is the only generally accepted environmental risk factor for RA, especially for seropositive RA in men [40], but research data also suggests other factors with either positive or negative association [41]. In Finland, the proportion of 25- to 65-year-old daily smokers has shown a decline both in men and women during this millennium [42]. This may have an

impact on the observed incidences. Obesity has been linked to PsA [43] and SpA [44]. Tendency towards increasing obesity had slowed down in the working aged Finnish population between 2007-12 compared to previous decades, but still 65 % of men and 46 % of women were overweight and 20 % were obese [45]. This may partially explain the rising trend in SpA or PsA, although causal relationships cannot be concluded from observational studies.

To summarize, we detected an increasing number of new IIRD cases during this millennium. The focus on early diagnosis and treatment may have had an influence on this trend. The treatment opportunities of most IIRDs have advanced since the year 2000. Also, the outcomes of many IIRDs seem to have improved causing less work disability, hospital stays, joint replacement surgery, as well as overall pain and suffering among these patients. On the other hand, the growing number of new IIRD cases means more patient monitoring in rheumatologic clinics and greater use of costly medicines; thus translate in an escalated burden impacting both on society and the health care system. Diagnostic modalities have developed and classification criteria have changed, and it is unclear to what extent we are treating milder diseases that we might not have even been diagnosed in the past. Since both the treatments as well as the outcomes of IIRDs have vast economic consequences for the societies, it is important to keep track of the burden caused by these diseases.

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First-year drug therapy of new-onset rheumatoid and undifferentiated arthritis: A nationwide register-based study

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RESEARCH ARTICLE Open Access

First-year drug therapy of new-onset rheumatoid and undifferentiated arthritis: a nationwide register-based study

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Abstract

Background: In this retrospective cohort study, we evaluated the drug therapies used for early rheumatoid (RA) and undifferentiated (UA) arthritis patients.

Methods: From a nationwide register maintained by the Social Insurance Institution, information on sex, date of birth, and date of special medicine reimbursement decision for all new Finnish RA and UA patients between 2011 and 14 were collected, and their DMARD (Disease Modifying Antirheumatic Drug) purchases during the first year after the diagnosis were analyzed.

Results: A total of 7338 patients with early RA (67.3% female, 68.1% seropositive) and 2433 with early UA (67.8% female) were identified. DMARDs were initiated during the first month after the diagnosis to 92.0% of the patients with seropositive RA, 90.3% with seronegative RA and to 87.7% with UA ($p < 0.001$). Respectively, 72.1, 63.4, and 42.9% of the patients ($p < 0.001$) purchased methotrexate; 49.8, 35.9, and 16.0% ($p < 0.001$) as part of a DMARD combination during the first month. By the end of the first year after the diagnosis, self-injected biologics were purchased by 2.6, 5.3 and 3.1% ($p < 0.001$) of them. Only 1.4, 2.6 and 3.0% ($p < 0.001$) of the patients were not receiving any DMARDs. During the first year, 83.4% of the seropositive RA patients had purchased methotrexate, 50.4% sulfasalazine, 72.1% hydroxychloroquine, and 72.6% prednisolone.

Conclusions: Currently, combination therapy including methotrexate is a common treatment strategy for early seropositive RA in Finland. Despite an easy access to biologics, these drugs are seldom needed during the first year after diagnosis.

Keywords: Rheumatoid arthritis, Undifferentiated arthritis, Antirheumatic drugs, Disease modifying, Biologic therapy

Background

All modern recommendations of drug therapy for rheumatoid arthritis (RA) underline the importance of early treatment aiming at remission and the key role of methotrexate (MTX). However, the role of the initial use of combinations of conventional synthetic disease modifying antirheumatic drugs (csDMARDs) causes dissension [1–3]. In Finland, the findings of the FIN-RACo and the NEO-RACo trials have influenced the clinical practice [4–7]. The national Current Care Guideline from the year 2015 advocates the initiation of three csDMARDs, the so-called FIN-RACo combination: MTX, sulfasalazine (SSZ), hydroxychloroquine (HCQ), and low-dose prednisolone (PRD) in early, active RA [8]. In the preceding versions in 2003 and 2009, however, the use of combination therapy was less rigorously recommended than in the current version.

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Undifferentiated arthritis (UA) is an inflammatory arthritis where no specific diagnostic criteria are fulfilled. In Finland there are no specific early arthritis clinics, nor distinct treatment recommendations for UA, but the active treat-to-target (T2T) principle has been followed in clinical practice [9].

Implementing recommendations in real life may sometimes be suboptimal, but eventually they do bring about improvement to the use of DMARDs [10]. The data on the modern DMARD prescription patterns in early RA is still scarce, and seldom detailed. In a review article of studies done in 2002–2013, the penetration of antirheumatic therapy was found to be better in cohorts treated by rheumatologists (77–98%) than in cohorts allegedly treated by a mix of physicians (39–63%) [11]. In addition, a patient may not always use the prescribed medication. In the present study we describe how Finnish patients with early RA or UA purchased DMARDs between 2011 and 2015.

Methods

Finland's National Health Insurance covers both Finnish and foreign citizens residing permanently in Finland. The costs of most medicines prescribed by a doctor for the treatment of a disease are partially reimbursed by the Social Insurance Institution (SII) either at basic, lower special, or higher special rate, depending on the duration and severity of the disease. Patients with chronic inflammatory rheumatic disorders can be granted a special reimbursement (SR) (reimbursement of 65 to 72% of the drug price) for antirheumatic drugs after filling a medical certificate to SII. This certificate must describe the diagnostic procedures, an ICD10 diagnosis, and prescribed medication and be written in a rheumatology clinic. The certificates are reviewed by an insurance physician of the SII before the special reimbursement is granted after approximately 2–4 weeks. At one transaction, up to 3 months' supply of medicines can be reimbursed. Since it is economically very much in the patients' interest, practically all Finnish patients with anti-rheumatic medication for chronic inflammatory rheumatic disorders are entitled to reimbursement, and the pharmacists encourage their customers to request it if the reimbursement has not been applied for. There is also an annual maximum limit of out-of-pocket costs, which in 2020 is set at EUR 578. If the patients exceed the annual maximum, they can get an additional reimbursement, which means that for the rest of the year, they only pay a EUR 2.50 co-payment for each reimbursable medicine. This is of the greatest importance when the patient is prescribed some of the expensive medications such as self-injected biologics.

Patient cohort

On grounds of the information in these medical certificates, SII maintains a nationwide register of the reimbursement decisions and the 3-digit ICD10 diagnoses behind them. From this register we assessed data collected between 1 January 2011 and 31 December 2014, and collected information on adult (> 16 years old) patients who, for the first time, had been granted a special reimbursement of medications for rheumatoid factor (RF) and/or anti-citrullinated peptide antibody (ACPA) positive (ICD-10 diagnosis M05) RA, RF and ACPA negative RA (M06), or UA (M13). The information included sex, date of birth, and the date of the reimbursement decision which is the index day in our study.

The SII maintains also a register on the drugs purchased from pharmacies and reimbursed according to the basic or the special rate. In this register, drugs are classified according to the Anatomical Therapeutic Chemical (ATC) code. The register also includes the amount of the drug and the date of purchase. From this register, we collected data on the drugs purchased by the study cohort for 31 days before the index day (to include medications possibly purchased before the reimbursement decision) and for up to 1 year after the index day. All csDMARDs, glucocorticoids and self-injected biologics were included in the analysis. The number of DMARD purchases by the end of the first year after the index date was evaluated in each diagnosis group, as well as among the patients who initiated the FIN-RACo combination (with or without PRD) or not. Our study does not include the small proportion of patients who have received intravenous biologicals in public hospitals at their cost, because these medications are not reimbursed and registered by the SII.

Statistical methods

Statistical comparisons between diagnoses were made by using the $\chi 2$ test. Multivariate analyses were performed to identify whether age and gender were associated with the initiation of DMARD therapy (versus no DMARDs) or with the initiation of combination therapy (versus monotherapy) within the first month after the index date in each diagnosis group separately.

Results

Between 2011 and 2014, altogether 9771 adult (> 16 years old) patients with a new inflammatory arthritis diagnosis were identified, 4998 patients with seropositive RA [67.0% female, mean (SD) age 58 (15) years]; 2340 with seronegative RA [67.7% female, 56 (17) years]; and 2433 with UA [67.8% female, age 49 (17) years].

The drugs purchased by the patients during the first month after the index day are presented in Table 1. The seropositive RA patients used more all, as well as MTX-based csDMARD-combinations, more MTX and prednisolone than the seronegative RA or UA patients. The use of any other csDMARDs than MTX, SSZ, or HCQ was rare during the first months in all patient groups,

Table 1 Numbers and proportions (%) of patients with seropositive rheumatoid arthritis (RA), seronegative RA and undifferentiated arthritis using various anti-rheumatic drugs and drug combination strategies by the end of the first month after arthritis diagnosis

	Seropositive rheumatoid arthritis $N = 4998$	Seronegative rheumatoid arthritis $N = 2340$	Undifferentiated arthritis $N = 2433$	*p*-value
Females N (%)	3349 (67.0)	1584 (67.7)	1650 (67.8)	
Mean age at diagnosis, years (SD)	58 (15)	56 (17)	49 (17)	
Combination strategies of DMARDs, N(%)				
Two DMARDs	1684 (33.7)	727 (31.1)	395 (16.2)	< 0.001
Three DMARDs	1118 (22.4)	255 (10.9)	77 (3.1)	< 0.001
MTX-based combination	2489 (49.8)	841 (35.9)	390 (16.0)	< 0.001
FIN-RACo combination*	1114 (22.3)	253 (10.8)	75 (3.1)	< 0.001
MTX + SSZ + HCQ + PRD	922 (18.4)	205 (8.8)	52 (2.1)	
MTX + SSZ + HCQ	192 (3.8)	48 (2.1)	23 (0.9)	
Medications				
Methotrexate (MTX)	3602 (72.1)	1483 (63.4)	1043 (42.9)	< 0.001
MTX per os	3428 (68.6)	1399 (59.8)	949 (39.0)	
MTX s.c.	174 (3.5)	84 (3.6)	94 (3.9)	
Sulfasalazine (SSZ)	2059 (41.2)	880 (37.6)	1121 (46.1)	< 0.001
Hydroxychloroquine (HCQ)	2272 (55.5)	940 (40.2)	472 (19.4)	< 0.001
Leflunomide	51 (1.0)	30 (1.3)	23 (1)	0.48
Azathioprine	29 (0.6)	11 (0.5)	14 (0.6)	0.83
Aurathiomalate	9 (0.2)	2 (0.1)	2 (0.1)	0.44
Auranofin	3 (0.1)	1 (0.0)	1 (0.0)	0.95
Cyclosporine	1 (0.0)	3 (0.1)	6 (0.3)	0.015
Prednisolone (PRD)	3025 (60.5)	1352 (57.8)	890 (36.6)	< 0.001
Self-injected biologics (all)	41 (0.8)	28 (1.2)	17 (0.7)	0.15
Etanercept	3 (0.06)	11 (0.47)	2 (0.08)	
Adalimumab	4 (0.08)	6 (0.27)	1 (0.04)	
Certolizumab	1 (0.02)	0 (0)	0 (0)	
Golimumab	3 (0.03)	1 (0.04)	0 (0)	
Abatacept	1 (0.02)	0 (0)	0 (0)	
No antirheumatic medication	401 (8.0)	227 (9.7)	300 (13.3)	< 0.001
Only prednisolone	85 (1.7)	63 (2.7)	46 (1.9)	0.61

*FIN-RACo combination: Methotrexate (MTX), sulfasalazine (SSZ), and hydroxychloroquine (HCQ) often combined with low-dose prednisolone (PRD)

and only a handful of patients started using self-injected biological DMARDs (bDMARDs) at this early phase.

As expected, during the first year the proportions of patients purchasing any csDMARDs increased, especially in the seropositive RA group (Table 2). MTX, SSZ, and HCQ remained the absolute most used drugs, followed by leflunomide (LEF) with approximately 5% of patients in each group having purchased it during the first year; all other csDMARDs having a much smaller share. Self-injected biologics were initiated by 5.3% of the seronegative RA patients, and less often in the two other patient groups ($p < 0.001$). Only 3% of the patients in the UA group had not purchased any DMARDs during the first year, in the other groups the proportion of patients with no medications was even smaller ($p < 0.001$).

The median numbers (IQR) of patients' DMARD purchases by the end of the first year after diagnosis are presented in Table 2. We further divided patients into two groups depending on whether they were initially treated with the FIN-RACo combination (MTX + SSZ + HCQ) or not. In the FIN-RACo group, the median (IQR) number of DMARD purchases was 18 (15 to 22) for seropositive RA, 19 (15 to 22) for seronegative RA, and 18 (15 o 24) for UA during the first year, whereas the respective numbers in the non-FIN-RACo group were 10 (6 to 13) for seropositive RA, 9 (6 to 13) for seronegative RA, and 7 (4 to 11) for UA. Thus, patients

Table 2 Numbers and proportions (%) of patients with seropositive rheumatoid arthritis (RA), seronegative RA and undifferentiated arthritis having used various anti-rheumatic drugs by the end of the first year after arthritis diagnosis. Also, the number of DMARD purchases by the patients during the first year after diagnosis is shown

	Seropositive rheumatoid arthritis $N = 4998$	Seronegative rheumatoid arthritis $N = 2340$	Undifferentiated arthritis $N = 2433$	*p*-value
Females N (%)	3349 (67.0)	1584 (67.7)	1650 (67.8)	
Mean age at diagnosis, years (SD)	58 (15)	56 (17)	49 (17)	
Number of DMARD purchases, median (IQR)	11 (7, 16)	10 (6, 14)	7 (4, 11)	< 0.001
Medications				
Methotrexate (MTX)	4167 (83.4)	1789 (76.4)	1512 (62.1)	< 0.001
MTX per os	3998 (80.0)	1706 (72.9)	1406 (57.8)	
MTX s.c.	625 (12.5)	308 (13.2)	310 (12.7)	
Sulfasalazine (SSZ)	2520 (50.4)	1090 (46.6)	1362 (56.0)	< 0.001
Hydroxychloroquine (HCQ)	3603 (72.1)	1357 (58.0)	866 (35.6)	< 0.001
Leflunomide	256 (5.1)	121 (5.2)	119 (4.9)	0.89
Azathioprine	65 (1.3)	31 (1.3)	23 (0.9)	0.37
Aurathiomalate	42 (0.8)	12 (0.5)	8 (0.3)	0.023
Auranofin	4 (0.1)	2 (0.1)	2 (0.1)	0.99
Cyclosporine	13 (0.3)	10 (0.4)	23 (0.9)	< 0.001
Prednisolone (PRD)	3626 (72.6)	1706 (72.9)	1283 (52.7)	< 0.001
Self-injected biologics (all)	131 (2.6)	125 (5.3)	76 (3.1)	< 0.001
Etanercept	53 (1.1)	55 (2.4)	31 (1.3)	
Adalimumab	40 (0.8)	48 (2.1)	29 (1.2)	
Certolizumab	23 0.5)	19 (0.8)	12 (0.5)	
Golimumab	19 (0.4)	19 (0.8)	9 (0.4)	
Abatacept	8 (0.2)	5 (0.2)	1 (0.04)	
Tocilizumab	4 (0.1)	1 (0.04)	1 (0.04)	
Ustekinumab	0 (0)	0 (0)	1 (0.04)	
No antirheumatic medication	71 (1.4)	60 (2.6)	73 (3.0)	< 0.001
Only prednisolone	25 (0.5)	30 (1.3)	24 (1.0)	< 0.001

in the FIN-RACo group had almost twice as many DMARD purchases as the rest of the patients.

In multivariate analyses, using age and gender as covariates, we found that gender did not predict whether DMARDs were initiated or not, or whether the patient was treated with combination therapy or monotherapy during the first month after the index date in any of the three diagnosis groups. Higher age was negatively associated with DMARD initiation within a month from diagnosis among UA patients [OR 0.99 (CI 0.98 to 0.99)] but not among RA patients. The initiation of combination therapy decreased with a rising age among seropositive RA patients [OR 0.99 (CI 0.98 to 0.99)] but not among other diagnosis groups.

Discussion

In Finland, early arthritis patients are mainly treated by rheumatologists. The Current Care Guideline advises general practitioners to refer all patients with suspected RA to specialist clinics. In addition, a rheumatologist's certificate is needed to apply special reimbursement for antirheumatic medication, by which we identified our cases. Consequently, our cohort includes those arthritis patients, who had been examined by rheumatologists and prescribed DMARDs and glucocorticoids. Obviously, all patients with UA are not included. These facts explain, why within one month from the index date more than 90% of the RA patients purchased DMARDs and nearly 70% MTX. In seropositive patients, the percentages were higher, and within one year, only 1.4% of the seropositive and 2.6% of the seronegative RA patients had not purchased any DMARDs. For the UA patients the DMARD coverage was slightly less. These numbers also suggest a good drug adherence among Finnish arthritis patients.

Our results may not be comparable with studies in other settings. In a Canadian cohort studying the DMARD treatment of 24,942 early RA patients during the year following the diagnosis in 1997–2006, only 21% of patients treated by a general practitioner received any DMARDs, but 67% of those treated by a rheumatologist did so [12]. In a Danish cohort of 1516 early RA patients studying the initiation of MTX between 1996 and 2006, only 21% of the patients received MTX within 90 days; though, in 13% of the patients another DMARD had been initiated [13]. In studies based on large RA cohorts from US commercial and Medicare claims databases, the initiation of DMARD treatment within one year after diagnosis decreased from 63 to 56% between the cohorts 2004–08 and 2009–12 [14, 15]. Another US study based on claims databases found that over half of the 63,101 RA patients identified did not receive DMARD treatment within 90 days after diagnosis [16]. In a smaller Canadian cohort of 204 early RA patients in 2003–06, only 23% were prescribed a DMARD within 3 months and 47% within 6 months [17]. Also, in a recent Italian cohort of 1336 RA patients, less than 40% of the patients had started treatment with MTX within 3–6 months from the diagnosis [18].

Better coverages are found in contemporary materials treated by rheumatologists. In the French ESPOIR cohort of 775 early inflammatory arthritis patients, 77% received at least one DMARD after a median of four months [19]. A Canadian study of 339 RA patients found that 92% of the patients began DMARD therapy within three months [20]. In a multicenter ERAN cohort in UK and Eire, DMARDs were prescribed to 97% of the 808 early RA patients; however, the median time of DMARD initiation was 8 months after the symptom onset [21]. An Italian study reported that 83% of 10,401 patients were prescribed a csDMARD at RA diagnosis but only 6% of them received combination therapy [22].

Our previous analysis of Finnish early RA patients between 2000 and 2007 showed that although at the beginning of the study period SSZ was the most commonly prescribed DMARD during the first 3 months after the diagnosis, at the end of the observation period (2006–07) it had given way to MTX (69%) and combination DMARDs (53%) as the initial treatment [23]. Our earlier results also demonstrated that the proportion of patients starting triple combination within the first month increased from 6 to 16% between 2000 and 07. Our current results confirm that there has been a further increase. However, only 22% of early seropositive RA patients commenced the triple therapy recommended in the latest 2015 Current Care Guideline [8]. The Finnish recommendations from 2009 favored the start of the triple therapy and low dose prednisolone only for patients with very active RA, but not automatically as the first choice in all patients. Also, real life patients diagnosed with RA have seldom as active disease as patients in clinical trials [24], and further, they may have comorbidities and polypharmacy contraindicating certain medications, thus it is possible that rheumatologists base their decisions more on T2T principle than on slavishly following certain recommendations [25]. Either way, since we are lacking data of the levels of activity of the patients' disease, further conclusions on whether only one-fifth of the patients had active disease requiring triple therapy cannot be drawn.

There is a distinction between guidelines encouraging a T2T strategy on the one hand and what actually happens in practice. In an ESPOIR cohort, where adherence to three of the EULAR recommendations concerning the start and early adjustment of DMARDs was studied, the adherence rate for all three recommendations was only 23% among early arthritis patients [26]. Still, among those patients whose treatment adhered to given recommendations, the risk of clinical and radiographic progression was lower. Knowing that the fulfilment of treatment guidelines in real life is always suboptimal, the strict national treatment recommendations, such as the recommendation of triple therapy initiation in early RA in Finland, will probably lead to optimal outcomes.

The number of DMARD purchases could reflect drug adherence although some patients may not always buy medication for the next three months as usually happens. In our analysis, the patients initiating the FIN-RACo combination had twice the number of DMARD purchases during the first year compared to those patients who did not start with the FIN-RACo combination. Frequent purchases suggest a regular drug usage and good survival rate of the FIN-RACo combination.

Two Finnish studies based on real life early arthritis patient cohorts have been published. The first one included 406 early RA or UA patients between 2008 and 11 [27]. Of the RA patients, at three months 20% were using triple therapy, 33% other MTX based combination, 36% MTX monotherapy, and 8% other DMARD monotherapy; for the UA patients the respective percentages were 6, 28, 43, and 17%, respectively. At one year, the proportions of RA patients using various medications had not changed markedly. In a more recent (2011–14) FIN-ERA cohort of 611 DMARD naïve early arthritis patients (506 RA and 105 UA patients) recruited in five Finnish outpatient rheumatology clinics, MTX-based combination therapy was initiated to 68% of the patients and the proportion of triple combination (MTX, SSZ and HCQ) was 31% [28]. These results, in line with our results, show that DMARD initiation for early arthritis patients is generally comprehensive in Finland.

In Finland there are no separate treatment recommendations for UA, but the active T2T principle is widely

used in clinical practice regardless of the diagnosis. The European League of EULAR recommendations for early arthritis in 2007 recommended for patients at risk of developing persistent and/or erosive arthritis a DMARD as early as possible, preferably MTX, even if no classification criteria for a specific disease are fulfilled [29]. The latest update of the recommendation in 2016 presented no major changes to these principles [9]. The fulfillment of the EULAR recommendations for the treatment of early arthritis was studied in 813 patients from the ESPOIR cohort between 2002 and 05; 78% of patients started a DMARD, 67% MTX and 52% reached remission [30]. In our material the DMARD initiation was more comprehensive, but the proportion on MTX lower; this might be explained by the fact that traditionally SSZ has been prescribed in seronegative oligoarthritis in Finland.

In our study, the use of self-injected biological DMARDs was more common among seronegative RA patients than seropositive RA or UA patients. Seronegative RA may be a heterogenous group of diseases, as shown in a recent 10-year observational study [31], thus explaining poorer treatment outcomes with csDMARDs and a greater need for switching to bDMARDs.

A shortcoming of this study is the lack of clinical data; we do not have information of the disease's activity at diagnosis, nor at follow-up. Further, we may miss patients that the physician intends not to treat. Nevertheless, the incidence of seropositive RA has remained stable throughout this millennium, that of seronegative RA has decreased slightly supposedly due to changed diagnostics, and for the same reason, the incidence of UA has increased [32]. Thus, it seems unlikely that we are missing many patients. However, since this is a register-based study and we lack the data on the duration of symptoms before the diagnosis, it is possible that the current study includes some patients that are diagnosed with a time lag; in these cases, DMARDs used represent patients' initial treatment rather than the treatment of early rheumatic disease. Also, we do not know how high a proportion of UA patients received a more specific diagnosis later; this could offer an interesting area for further research. Further, in the lack of clinical data it is possible that a certain proportion of the UA patients in our study may not be comparable to patients in so called early arthritis clinics, but have a chronic inflammatory arthritis requiring specific anti-rheumatic drug therapy.

Even though we do not have any clinical outcome measures, the initiation of self-injected biologics served as a surrogate marker of treatment failure. We were expecting to see that patients having received combination DMARDs as their first treatment, and thus judged by their treating rheumatologist to have an active disease to be the ones to end up starting a biologic earlier and more often than other patients, but at least during the first year that was not the case. Thus, at least in the early phase, combination DMARD treatment appears to be effective.

Although we are lacking the data on infusion based biological drugs, only a small proportion of patients are initiating them during the first year after the diagnosis, the time period of interest in our study. According to the Finnish ROB-FIN register study, in 2004–14 the first TNF-inhibitors were initiated to RA patients after a median (IQR) of 8.2 (2.4–17) years of disease duration, most often with adalimumab (39%) or etanercept (39%), while infliximab was a rarer choice (12%) [33]. According to the most recent, yet unpublished, ROB-FIN register data from 2010 to 15, the use of infliximab as the first biologic had decreased from 7.5 to 4.2% for RA patients (Kalle Aaltonen, personal communication). Rituximab was the first choice for as many as 20–23% of the RA patients. Still, the majority started self-injected drugs, and the median (IQR) point of starting the first biologic was after 10 (4.4–18) years of disease duration. Consequently, our results of the first year treatment would hardly have changed markedly, were the infusion-based drugs included.

Conclusions

In this study we wanted to describe the drug therapies used for early rheumatoid (RA) and undifferentiated (UA) arthritis patients between 2011 and 2015. The rheumatologist-based treatment received by the Finnish new-onset arthritis patients is early initiation of cDMARDs, mainly MTX, and often in combinations.

Abbreviations

ACPA: Anti-citrullinated peptide antibody; ATC: Anatomical Therapeutic Chemical; bDMARDs: Biological DMARDs; csDMARD: Conventional synthetic disease modifying antirheumatic drug; EULAR: European League Against Rheumatism; FIN-RACo: The Finnish Rheumatoid Arthritis Combination Therapy Trial; HCQ: Hydroxychloroquine; LEF: Leflunomide; MTX: Methotrexate; PRD: Prednisolone; RA: Rheumatoid arthritis; RF: Rheumatoid factor; ROB-FIN: The National Register for Biologic Treatment in Finland; SII: Social Insurance Institution; SR: Special reimbursement; SSZ: Sulfasalazine; UA: Undifferentiated arthritis; T2T: Treat-to-target

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Authors' contributions

PM, VR, HK, LV, and KP have participated in the conception and design of the study, and have contributed to the interpretation of the results. KP and LV contributed to the acquisition of data. HK conducted the statistical analyses. PM and VR were the main contributors in writing the manuscript, but all authors (PM, VR, HK, LV, JE, and KP) contributed to critical revision of the manuscript. All authors have read and approved the final manuscript before submission.

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Availability of data and materials
The data that support the findings of this study are available from the Social Insurance Institution (SII) of Finland but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the SII.

Ethics approval and consent to participate
Only unidentifiable register data were used and patients were not contacted, thus the Finnish legislation did not require an approval by an ethics committee.

Consent for publication
Not applicable.

Competing interests
Dr. Muilu reports a Congress trip from UCB Pharma, a Congress trip from MSD Finland and a congress trip from Sanofi Genzyme outside the submitted work. Dr. Rantalaiho reports a speaker's honorarium and a congress trip from Pfizer, a congress trip from Celegen and a congress trip from Mylan outside the submitted work. Dr. Puolakka, Dr. Virta, Dr. Eriksson, and Mr. Kautiainen have nothing to disclose.

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PUBLICATION III

Opioid use among patients with early inflammatory arthritides compared to the general population

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Opioid Use among Patients with Early Inflammatory Arthritides Compared to the General Population

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ABSTRACT. ***Objective.*** To assess to what extent the worldwide opioid epidemic affects Finnish patients with early inflammatory arthritis (IA).

Methods. From the nationwide register maintained by the Social Insurance Institution of Finland, we collected all incident adult patients with newly onset seropositive and seronegative rheumatoid arthritis (RA+ and RA–) and undifferentiated arthritis (UA) between 2010 and 2014. For each case, 3 general population (GP) controls were matched according to age, sex, and place of residence. Drug purchases between 2009 and 2015 were evaluated 1 year before and after the index date (date of IA diagnosis), further dividing this time into 3-month periods.

Results. A total of 12,115 patients (66% women) were identified. At least 1 opioid purchase was done by 23–27% of the patients 1 year before and 15–20% one year after the index date. Relative risk (RR) of opioid purchases compared to GP was highest during the last 3-month time period before the index date [RR 2.81 (95% CI 2.55–3.09), 3.06 (2.68-3.49), and 4.04 (3.51–4.65) for RA+, RA–, and UA, respectively] but decreased after the index date [RR 1.38 (1.23–1.58), 1.91 (1.63–2.24), and 2.51 (2.15–2.93)]. Up to 4% of the patients were longterm users both before and after the diagnosis.

Conclusion. During 2009–15 in Finland, opioid use peaked just before the diagnosis of IA but decreased rapidly after that, suggesting effective disease control, especially in seropositive RA. Further, opioids were used to treat arthritis pain of patients with incident RA and UA less often than previously reported from other countries. (J Rheumatol First Release April 1 2020; doi:10.3899/jrheum.190355)

Key Indexing Terms:
RHEUMATOID ARTHRITIS — UNDIFFERENTIATED ARTHRITIS
OPIOID ANALGESICS — PAIN

Drug therapy outcomes in inflammatory arthritis (IA) have improved during the past 2 decades; however, arthritis pain management remains a challenge[1,2]. Arthritis pain is often multifactorial, including inflammation and irreversible joint degeneration, and patients with IA may also have abnormalities in central pain processing or several comorbidities that induce pain[3,4]. Patients with rheumatoid arthritis (RA) consider pain relief as the most important area of health improvement and it is also their most common motive for seeking medical consultation[5,6].

Nonsteroidal antiinflammatory drugs (NSAID) are considered first-line analgesics in IA[6,7], but increasing evidence of gastrointestinal, cardiovascular, and kidney-related side effects have reduced their use[8,9]. Pain-relieving effects of NSAID may improve when used in combination with paracetamol (acetaminophen); however, adverse effects rise simultaneously[10]. The followup periods in studies investigating the effectiveness of opioids in arthritis or musculoskeletal-related pain are often short in duration[1,11,12,13,14]. These studies usually emphasize the risks of adverse effects and do not support the benefits of longterm opioid treatment or the use of strong opioids[1,11,12,13,14]. In addition to well-known harm outcomes such as addiction among patients with RA, exposure to opioids has been shown to increase the risk of serious infections linked to hospitalizations[15] or nonvertebral fractures mostly related to falls[16], and cause

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delay in the initiation of disease-modifying antirheumatic drugs (DMARD) for the treatment of RA[17]. Current recommendations thus state that opioids should be used only after careful consideration in IA[1,7].

The rather liberal management of chronic nonmalignant pain has partially contributed to the current worldwide opioid epidemic. Most of the literature on the current opioid epidemic, however, comes from the United States, and to our knowledge, there are few epidemiological reports on opioid use from the Nordic countries[18,19,20] and none in the setting of inflammatory rheumatic diseases. In this analysis, we wanted to assess what happens in the setting of early IA, where the pain in an undiagnosed disease is a true problem, but the need for pain medication should decline quickly when accurate antirheumatic treatment is given.

MATERIALS AND METHODS

The Finnish social security system is organized by the Social Insurance Institution (SII) and provides all permanent residents in Finland a variety of benefits. The costs of most medicines prescribed by a doctor for the treatment of a disease are partially reimbursed by SII, either at a basic, lower special, or higher special rate, depending on the disease and its severity. Patients with chronic IA can be granted a special reimbursement (SR; reimbursement of 65–72% of the drug price) for antirheumatic drugs after filling out a medical certificate to SII. This certificate must describe the diagnostic procedures and prescribed medication and be written in a rheumatology clinic. SII maintains a register on these SR, including patients' age, sex, International Classification of Diseases, 10th revision (ICD-10) code of the disease, and date of entitlement.

From these national registry data we collected all incident adult patients (aged ≥ 18 yrs) granted the first SR for medications of either seropositive RA, seronegative RA, or UA from January 1, 2010, to December 31, 2014. The patients were identified with an ICD-10 code: seropositive RA (M05), seronegative RA (M06), and UA (M13). The dates (month and year) when the decision regarding the special refund for antirheumatic drugs took effect was used as a proxy indicator of the date of IA diagnosis, that is, the index date in our study.

For each incident case, 3 eligible controls were randomly selected from the Population Register Centre and were individually matched to the cases by age, sex, and place of residence. Also, adjustments by education levels (basic, middle, lower high, and upper high level) were performed. Those persons among controls that had been granted SR for any IA before year 2010 were excluded.

Drug purchases of analgesics between 2009 and 2015 were obtained from the Drug Purchase Register. This register, also maintained by SII (since 1994), covers all drug purchases prescribed by physicians (a prescription is mandatory for opioids) and reimbursed by National Sickness Insurance Scheme in Finland. These data include information on drug class, quantity, and date of dispensing. Drugs are categorized according to the Anatomical Therapeutic Chemical Classification System, developed by the World Health Organization for drug consumption statistics. Our main focus was on opioids [N02A; mild opioids (codeine combination products and tramadol), moderate opioids (buprenorphine), and strong opioids (morphine, hydromorphine, oxycodone, and fentanyl)], but we also analyzed the purchases of NSAID (M01A) and paracetamol (N02BE01). We restricted our analysis to drug purchases starting from 2009 because of inconsistent reimbursement of codeine combination products (the most frequently used opioid in Finland) before that. Drug purchases were evaluated 1 year before and after the index date, further dividing the observation time into 3-month time periods. The drug reimbursement regulations (of the National Sickness Insurance Scheme) restrict the refunded drug supply period to a maximum of 3 months per purchase. Longterm opioid use was defined as at least 1 opioid purchase in 3 or 4 quarters per year, and in that analysis all opioids from mild to strong were included, together, 1 year before and 1 year after the index date.

Statistical methods. Statistical comparisons between the cases and controls were made using the chi-square test or generalized linear models with binomial family and log link. Longitudinal measures were analyzed using generalizing estimating equations models with the unstructured correlation structure with appropriate distribution and link function. Stata 15.1 (StataCorp LP) statistical package was used for the analysis.

Ethical considerations. Permission to use databases was obtained from the SII. In accordance with Finnish legislation, approval by an ethics committee and informed consent are not required for register-based studies done without contacting the study subjects.

RESULTS

A total of 12,115 adult patients with either seropositive RA, seronegative RA, or UA were identified. Of these, 6186 patients (66% women) had seropositive RA, 2970 patients (67% women) had seronegative RA, and 2959 patients (67% women) had UA. The mean ages (SD) at diagnosis were 58 (15), 57 (17), and 49 (17) years for seropositive RA, seronegative RA, and UA, respectively. One percent of the controls and 0.9% of the patients died during the first year after the index date. In these cases, patients were followed until their death.

The proportion of opioid, NSAID, and paracetamol purchasers among patients with RA and UA and their controls during the year before and after the index date, further dividing the observation time into quarters, is shown in Figure 1. The opioid purchases peak during the last 3-month period before the index date in all diagnosis groups. The drop in opioid purchases among patients took place rapidly after the index date when antirheumatic medication was presumably initiated; a similar drop did not exist in the control groups. After this drop, the frequency of opioid use leveled off and no significant decrease was further seen in any diagnosis groups during the observation time. Still, 1 year after the index date, patients with IA purchased more opioids than did controls, this difference being most evident in UA. The use of NSAID and paracetamol was more common both in IA groups and in the general population (GP) than the use of opioids, but also their purchases peaked among IA but not among controls in a similar way as seen in opioids (Figure 1).

Figure 2 shows the risk ratio (RR) of opioid purchases among RA and UA patients 1 year before and after the index date by quarters compared to their controls. In RA, the RR gradually increased before the index date and was highest during the last quarter before the index date (RR 2.81, 95% CI 2.55–3.09 for seropositive RA and 3.06, 95% CI 2.68–3.49 for seronegative RA), but decreased rapidly after the index date, especially in seropositive RA (RR 1.38, 95% CI 1.23–1.58) but also in seronegative RA (1.91, 95% CI 1.63–2.24). Patients with UA were up to 4 times more likely (RR 4.04, 95% CI 3.51–4.65) opioid purchasers than

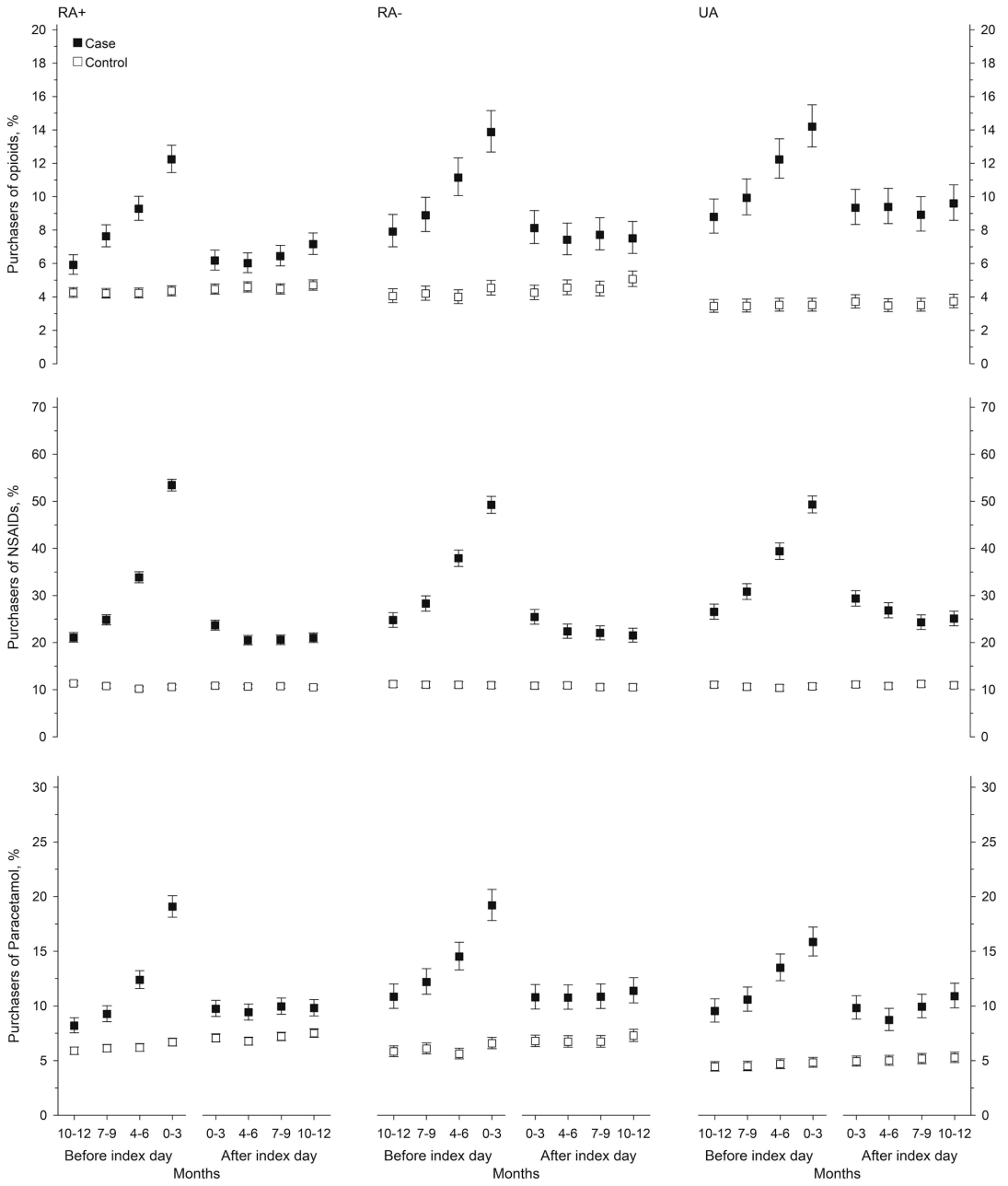

Figure 1. The proportion (%) of opioid, NSAID, and paracetamol purchasers among patients with seropositive RA (RA+), seronegative RA (RA–), and UA and their controls 1 year before and after the index date (the date when special reimbursement for antirheumatic drugs became effective). The index date is shown in the middle of the X-axis, and the 2-year observation time has been divided into 3-month periods. NSAID: nonsteroidal antiinflammatory drug; RA: rheumatoid arthritis; UA: undifferentiated arthritis.

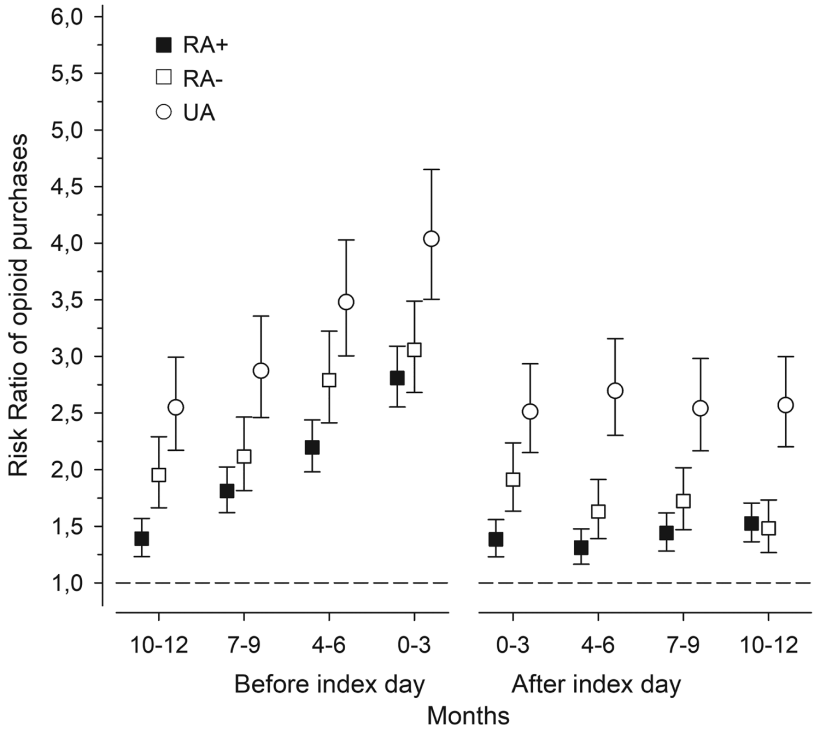

Figure 2. The risk ratio of opioid purchases among patients with seropositive RA (RA+), seronegative RA (RA–), and UA compared to their controls 1 year before and after the index date (the date when special reimbursement for antirheumatic drugs became effective). The index date is shown in the middle of the X-axis, and the observation time has been divided into 3-month periods. RA: rheumatoid arthritis; UA: undifferentiated arthritis.

their controls during the last quarter before the index date, and still a 2.5-fold difference (RR 2.51, 95% CI 2.15–2.93) remained during the whole first year after the index date.

Table 1 shows the proportions of any opioid purchasers as well as longterm users (as defined in the Methods section) during the whole year before and after the index date. Longterm opioid use was more common among patients with IA both before and after the index date compared to their controls. After the index date, patients with UA seem more likely (RR 3.5) to be longterm opioid users than do patients with RA (RR 1.3 and 1.9 for seropositive and seronegative RA, respectively), although they were substantially younger at diagnosis than patients with RA. Instead, in the control population, longterm opioid use increased with rising age. Based on the differences in the proportions of opioid purchasers among cases and controls, about 1–4% of patients with IA seem to use opioids over the long term for their arthritis pain. The relative risk did not differ significantly between the years before or after the index date in any of the 3 diagnosis groups, indicating that longterm opioid use may stabilize early in the disease course. The RR were slightly lower across the board when adjusted by the education level.

The majority of purchased opioids were mild opioids in all diagnosis groups (Figure 3). Mild opioids were purchased most frequently by patients with UA; of these, 32.4% had at least 1 purchase during the 2-year observation time. Patients with IA purchased more opioids of any type (mild, moderate, or strong) compared to controls, and the difference reached statistical significance in all groups with the exception of seropositive RA, where arthritis pain seems not to be treated by strong opioids (Figure 3).

The only group in which opioid purchases differed between men and women was seropositive RA during the year before the index date, where 25.3% (95% CI 23.4–27.2) of men purchased opioids compared to 21.4% (95% CI 20.2–22.7) of women ($p < 0.001$). No sex differences were seen in the control groups.

DISCUSSION

Our study shows that opioids were used at least once by 23% of seropositive RA, 25% of seronegative RA, and 27% of patients with UA during the year preceding the diagnosis, and by 15% of seropositive RA, 16% of seronegative RA, and 20% of UA patients during the year following the diagnosis, whereas on average 11% of the controls of patients

Table 1. The proportion of individuals who purchased opioids at least once or were longterm opioid users, among patients with seropositive rheumatoid arthritis (RA+), seronegative RA (RA–), and undifferentiated arthritis (UA) and their controls 1 year before and after the index date (the date when special reimbursement for antirheumatic drugs became effective).

Variables	Case, % (95% CI)	Control, % (95% CI)	RR (95% CI) Crude	RR (95% CI) Adjusted
Any opioid purchase				
RA+				
Before	22.7 (21.7–23.8)	9.8 (9.4–10.2)	2.32 (2.18–2.47)	2.27 (2.13–2.42)
After	15.4 (14.5–16.3)	10.9 (10.5–11.4)	1.41 (1.31–1.51)	1.38 (1.28–1.48)
RA–				
Before	25.0 (23.4–26.5)	10.1 (9.5–10.8)	2.47 (2.26–2.69)	2.43 (2.23–2.66)
After	16.4 (15.1–17.7)	11.3 (10.6–12.0)	1.45 (1.31–1.60)	1.42 (1.29–1.57)
UA				
Before	26.5 (24.9–28.1)	8.9 (8.3–9.5)	2.97 (2.72–3.25)	2.94 (2.68–3.21)
After	19.7 (18.3–21.2)	9.5 (8.9–10.2)	2.07 (1.88–2.28)	2.04 (1.85–2.24)
Longterm opioid users				
RA+				
Before	3.2 (2.8–3.7)	2.2 (2.0–2.4)	1.46 (1.24–1.73)	1.40 (1.19–1.66)
After	3.3 (2.9–3.8)	2.5 (2.2–2.7)	1.34 (1.14–1.58)	1.29 (1.09–1.51)
RA–				
Before	4.7 (4.0–5.5)	2.0 (1.7–2.3)	2.33 (1.87–2.90)	2.26 (1.82–2.81)
After	4.6 (3.9–5.4)	2.4 (2.1–2.8)	1.89 (1.53–2.33)	1.83 (1.48–2.26)
UA				
Before	5.4 (4.6–6.3)	1.5 (1.2–1.7)	3.67 (2.92–4.61)	3.57 (2.85–4.49)
After	5.5 (4.7–6.4)	1.6 (1.3–1.9)	3.46 (2.77–4.33)	3.37 (2.70–4.21)

Risk ratios (RR) for any opioid purchase and longterm opioid use are given. The controls were individually matched to the cases regarding age, sex, and place of residence. The adjustment by the education level is also shown.

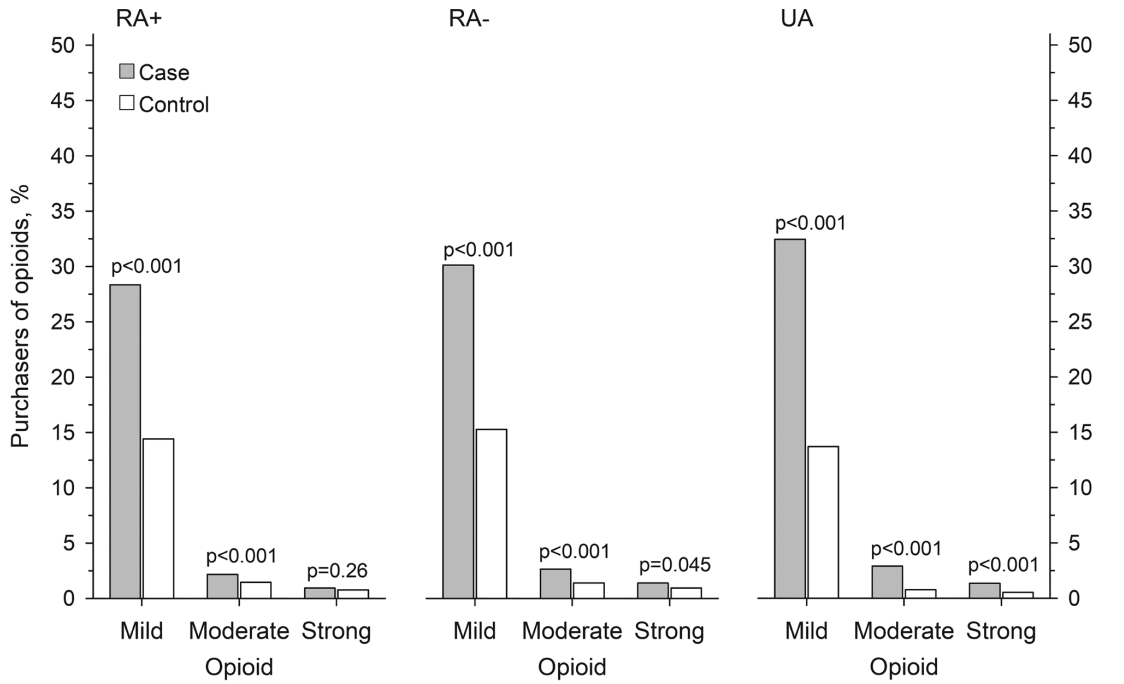

Figure 3. The distribution of opioid purchasers by the opioid type (mild, moderate, strong) among patients with seropositive RA (RA+), seronegative RA (RA–), and UA during the 2-year observation period. For each diagnosis group, the results are compared to controls adjusted for age, sex, and place of residence. Patients having combined use of different opioid types are shown in all groups in question. RA: rheumatoid arthritis; UA: undifferentiated arthritis.

with RA and 9% of the controls of patients with UA had at least 1 opioid purchase during the 2-year observation period. Opioid purchases reached the highest levels just before the index date in all 3 diagnosis groups. Longterm opioid use was also more common among the patients; during the first year after diagnosis, patients with seropositive RA were 1.3 times, patients with seronegative RA 1.9 times, and patients with UA 3.5 times more likely longterm opioid users than their controls from the GP. In our trial, the vast majority of opioids purchased were mild in all groups.

In our study, opioid use especially among patients with seropositive RA decreased rapidly once the diagnosis had been set, presumably indicating initiation of antirheumatic drugs and effective disease control with DMARD. The same progress was seen in seronegative RA and somewhat less sharply in UA. In all diagnoses the purchases of NSAID and paracetamol showed similar trends, even though the percentages of patients purchasing these medications were markedly higher.

Thus the decrease in pain medication purchases in UA was less marked after the diagnosis of the inflammatory disease than in RA. Also, according to current results, patients with UA had a higher risk of using opioids throughout the whole year before and after the diagnosis than did patients with RA. The difference was even more marked when taking into account that the patients with UA were about 8–9 years younger at diagnosis than the patients with RA, while in the GP, opioid use became more common with rising age. We can only speculate on the possible reasons. Controlling arthritis pain may be more challenging in UA than in RA, possibly owing to somewhat less aggressive initial antirheumatic medication (unpublished data). Patients with seronegative RA have been shown to experience higher disease activity and delayed remission, partly because of changed diagnostics and the requirement for more joint involvement at diagnosis[21], which may partly explain the differences in opioid use between the 2 RA serotypes. Further, patients with seronegative RA and UA may actually have another condition, such as crystal arthropathy, osteoarthrosis, or hemochromatosis that may not respond to traditional DMARD, which explains why those groups had more need of pain medication than do the seropositives.

We also demonstrated that longterm opioid use after the index date was most common among patients with UA (6%) and least common among patients with seropositive RA (3%). Among the controls of patients with UA and RA, longterm opioid use was around 2% during the study period. No statistically significant differences were seen in the frequencies of longterm opioid use between the years before and after the index date in any of the 3 diagnosis groups, suggesting that those who end up being longterm users will continue to use opioids chronically even after initiation of DMARD treatment. This is an important finding and highlights the risk for opioid addiction. Similarly, patients with osteoarthritis who undergo joint replacement surgery, and thus should be pain-free after some time postoperatively, are at risk of prolonged opioid use at least 12 months after surgery if they have used opioids preoperatively[22]. Thus, contraindication for NSAID, painful comorbidities, and wrong diagnoses may lead to harmful longterm use of opioids.

Only a few studies have reported opioid use frequency in IA and these studies have focused specifically on RA[17,23,24,25,26]. Most of these studies are from the United States, where opioid consumption has reached epidemic levels during the past decades. Studies performed in a single medical center there compared RA (diagnosed at least 10 yrs earlier) with non-RA and showed that opioid use was higher in the RA group; in 2014, the rate of any opioid use was 40% and chronic use (defined as prescriptions for ≥ 60 days within a 6-month period or those individuals using extended-use formulations) was 12%[23]. A study based on data from the Corrona registry explored the frequency of self-reported chronic opioid use among 33,739 patients with RA, and found that chronic use rate, defined as any opioid use reported during ≥ 2 clinic visits that occurred once every 3 months, was 7% in 2002 and 17% in 2015[24]. Another study from the United States based on Medicare data between 2006 and 2014 showed that the proportion of regular opioid users, defined as those with ≥ 3 filled prescriptions or ≥ 1 opioid prescription filled for at least a 90-day supply for every 12-month period, has slightly declined after 2010, although was still 41% by 2014[25]. Even higher numbers were shown in a US study based on a large claims database between 2006 and 2014; this study identified 63,101 newly diagnosed patients with RA and reported that the proportions of any opioid users and chronic opioid users (those who received ≥ 180 days' supply of opioid medication during an average of 3.5 ± 2.1 yrs of followup) were 72% and 25% among the patients who received DMARD therapy versus 57% and 19% among those who did not[17]. According to our unpublished results, more than 97% of the patients with RA and UA purchased DMARD during the first year after the diagnosis. In a German study including a total of 3140 RA patients, any opioid use rate ranged from 6% to 33% in the year 2015 depending on the reported pain levels; these proportions were closer to numbers found in our study[26]. Recently, a single study from the United States showed that in addition to patients with RA, opioid use was also common among patients with ankylosing spondylitis (AS); about one-quarter of the AS patients in the commercial claims database group and more than three-quarters of the patients in the Medicaid population were reported to have chronic opioid use (defined as ≥ 90 days of drug supply)[27].

Socioeconomic status has been shown to have an effect on opioid use[28,29], but when we adjusted our results according to the education level, the effect was low.

The majority of opioids purchased by patients with RA

or UA in our study were mild opioids. Even though we do not face a similar problem with strong opioids compared to some Western countries, all opioids, even weak ones, are potentially addictive, and may be used, for example, in combination with alcohol or other drugs, and therefore should only be prescribed for valid indications. In Finland, the consumption rate of strong opioids has shown a subtle rising trend during recent years; still, the definite majority of prescribed opioids in Finland are mild opioids, especially codeine combination products[30]. In 2009 in Finland, the total consumption of opioids was 16.5 defined daily doses (DDD)/1000 inhabitants (inh)/day, whereas in 2015 the consumption was 15.6 DDD/1000 inh/day; in 2017 it had further decreased (14.9 DDD/1000 inh/day)[30].

It is noteworthy that our study probably describes the physicians' prescription patterns even more than their patients' opioid need or use. The controls from the GP as well as patients before IA diagnosis usually receive their drug prescriptions from primary care physicians, whereas patients who receive IA diagnosis and are started on DMARD are usually monitored in rheumatologic clinics at least the first 2 years after diagnosis and also get their drug prescriptions from there. Our study showed the drop in opioid use after diagnosis when patients were presumably monitored by rheumatologists, but the numbers did not reach population levels during the 1-year followup. In a US study, almost 50% of patients with RA who used opioids had received their opioid prescriptions from a rheumatologist[25].

The main strength of our study is its nationwide scope and the availability of high-quality public registries. The study includes basically all Finnish patients with early IA who are started on DMARD. The patient identification is based on diagnoses (ICD-10 codes) formulated by qualified specialists or special clinics. In Finland, opioids are available only by prescription, and are thus inclusively covered in the register we used. Also, inclusion of population controls strengthens the study and allows estimation of opioid use for arthritis pain, although we lack detailed indications of analgesics therapy.

The limitations of our study include the lack of clinical and health behavior data. Moreover, we have no data on the activity of IA or patient-level pain scores. Further, both NSAID and paracetamol can also be purchased over the counter, and those purchases are not covered in the Drug Purchase Register. However, although our report underestimates NSAID and paracetamol consumption, it is likely to be equal for both patient and control groups, and thus does not cause a substantial bias. We were not able to record the drugs used during possible hospital stays, but in Finland IA treatment is basically outpatient-based so this should not cause too large a bias. Finally, we do not know confidently whether the patients or GP used their purchased medications as prescribed.

Among newly diagnosed patients with IA, the use of opioids for arthritis pain during 2009–2015 in Finland was less common compared to reports from some Western countries, and it is concentrated on mild opioids. The use of opioids seems to decrease when patients receive the IA diagnosis and are started on DMARD, especially among seropositive patients with RA.

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PUBLICATION IV

Opioid use frequency in early axial spondyloarthritis in Finland - a pharmacoepidemic register study

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