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EFFICACY, SAFETY AND CLINICAL OUTCOMES OF BIOLOGIC DRUGS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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ACADEMIC DISSERTATION

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To the memory of Professor Yrjö T. Konttinen

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Aaltonen KJ, Virkki LM, Malmivaara A, Konttinen YT, Nordström DC, Blom M. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. *PLoS One* 2012;7:e30275. doi:10.1371/journal.pone.0030275

II Aaltonen KJ, Sokka T, Möttönen T, Korpela M, Komulainen R, Uusitalo T, Salomaa S, Uutela T, Valleala H, RAMI Study Group. A nationwide cross-sectional overview of patients with rheumatoid arthritis followed in outpatient specialty clinics in Finland. *Scand J Rheumatol* 2014;43:1–19. doi:10.3109/03009742.2013.876512

III Aaltonen KJ, Joensuu JT, Virkki L, Sokka T, Aronen P, Relas H, Valleala H, Rantalaiho V, Pirila L, Puolakka K, Uusitalo T, Blom M, Konttinen YT, Nordstrom D. Rates of Serious Infections and Malignancies Among Patients with Rheumatoid Arthritis Receiving Either Tumor Necrosis Factor Inhibitor or Rituximab Therapy. *J Rheumatol* 2015;42:372–8. doi:10.3899/jrheum.140853

IV Aaltonen KJ, Virkki LM, Jämsen E, Sokka T, Konttinen YT, Peltomaa R, Tuompo R, Yli-Kerttula T, Kortelainen S, Ahokas-Tuohinto P, Blom M, Nordström DC. Do biologic drugs affect the need for and outcome of joint replacements in patients with rheumatoid arthritis? A register-based study. Semin Arthritis Rheum 2013;43:55–62. doi:10.1016/j.semarthrit.2013.01.002

The studies are referred to in the text by their Roman Numerals (I-IV). The original publications are reprinted with the permission of the copyright holders.

ABBREVIATIONS

ACR = American College of Rheumatology

ADA = Adalimumab

Anti-CCP = Anti-Cyclic Citrullinated Peptide

bDMARD =Biologic Disease-Modifying Anti-Rheumatic Drug

CER = Certolizumab pegol

CDAI = Clinical Disease Activity Index

CI = Confidence interval

CRP = C-Reactive Protein

DDD = Daily Defined Dose

DMARD = Disease-Modifying Anti-Rheumatic Drug

EULAR = European League Against Rheumatism

ESR = Erythrocyte Sedimentation Rate

ETA = Etanercept

GH = (Patients assessment of) General Health

GOL = Golimumab

HAQ = Health Assessment Questionnaire

HCQ = Hydroxychloroquine

INF = Infliximab

MTX = Methotrexate

OA = Osteoarthritis

PRO = Patient-Reported Outcome

PSM	= Propensity Score Matching
RA	= Rheumatoid Arthritis
RAMI	=Reuman Aktiivisuuden MIttaaminen (Measurement of disease activity in arthritis)
RCT	= Randomized Clinical Trial
RF	= Rheumatoid Factor
ROB-FIN	= National Register for Biologic Treatment in Finland
SDAI	= Simplified Disease Activity Index
sDMARD	= Synthetic Disease-Modifying Anti-Rheumatic Drug
SJC	= Swollen Joint Count
SSZ	= Sulfasalazine
THR	= Total hip replacement
TJC	= Tender Joint Count
TJR	= Total joint replacement
THL	=Terveyden ja hyvinvoinnin laitos (National Institute for Health and Welfare)
TKR	= Total knee replacement

ABSTRACT

Background: Rheumatoid Arthritis (RA) is an autoimmune disease, which is treated with anti-inflammatory and immunosuppressive medication. The aim of the treatment is clinical remission. Starting from late 1990's biologic disease-modifying anti-rheumatic drugs (bDMARDs) have been used to treat patients with insufficient treatment response or intolerance to synthetic DMARDs (sDMARDs). Despite numerous randomized clinical trials (RCTs) conducted so far, only few studies comparing biologic drugs to one another exist. Furthermore, the patients eligible for RCTs may not fully represent the population exposed to biologics in routine healthcare. Additionally, some clinical outcomes or adverse effects may be too rare or delayed to be studied in an experimental RCT setting. Finally, there is limited information on the utilization of biologic treatments available in Finland.

Objectives: The objective of the thesis was to study the efficacy, clinical outcomes and adverse events of the biologic drugs in treatment of rheumatoid arthritis.

Methods: All published randomized controlled trials studying the efficacy and safety of biologic drugs based on the inhibition of tumor necrosis factor (TNF) were identified, evaluated and pooled in using a systematic review including a meta-analysis. Then we pursued a cross-sectional overview on the disease activity and medical treatment of patients with RA treated in the Finnish specialized healthcare. Finally, we executed two cohort studies in which we combined longitudinal patient data with information on the incidence of serious infections, malignancies and joint replacement operations retrieved from national registers.

Results: Forty-one articles reporting on 26 RCTs of TNF-inhibitors were included in the systematic review and meta-analysis. Five RCTs studied infliximab, seven etanercept, eight adalimumab, three golimumab and three certolizumab pegol. TNF-inhibitors as a monotherapy were more efficacious than placebo at all time points but were comparable to methotrexate (MTX). TNF-inhibitor and MTX combination was superior to either MTX or TNF-inhibitor alone. Increasing doses did not improve the efficacy. TNF-inhibitors were relatively safe compared to either MTX or placebo. The cross-sectional study revealed 91% of patients as concurrent users of synthetic disease-modifying anti-rheumatic drugs (sDMARDs). A triple therapy of MTX, hydroxychloroquine (HCQ), and sulfasalazine (SSZ) was used by 15%, other MTX-based combination by 30%, MTX alone by 20%, and other DMARDs alone or in combination by 26% of patients. In addition, glucocorticoids and biologics were used by 58% and 21% of patients, respectively. Of the 184 biologics users, 18% were not using sDMARDs concomitantly. The adjusted incidence rate ratios (aIRRs)

of infections compared to sDMARD users were 1.2 (95% CI 0.63-2.3), 0.84 (95% CI 0.53-1.3), 0.98 (95% CI 0.60-1.6) and 1.1 (95% CI 0.59-1.9) for the users of infliximab, etanercept, adalimumab and rituximab, respectively. The crude rates of malignancies were highest among the users of sDMARDs and rituximab and lowest among infliximab-treated patients with no differences in aIRRs. There were more primary joint replacement operations per 100 patient years among the users of biologic drugs (3.89, 95% CI 3.41–4.41) vs. DMARD (2.63, 2.35–2.94) users but slightly fewer revisions (0.65, 0.46–0.88 vs. 0.83, 0.68–1.01). Biologics users were more likely to receive a joint replacement to small joints ($p < 0.001$). The survival of the prostheses installed during or prior to follow-up was similar in both treatment groups.

Conclusions: Pooled data from RCTs showed that the safety of TNF-inhibitors is comparable to sDMARDs and only few differences were observed between individual agents. TNF-inhibitors are more efficacious in combination with MTX when compared against monotherapy with either TNF-inhibitors or MTX alone. Currently, more than 20% of Finnish RA patients are using biologic drugs, with a majority of them in combination therapy with sDMARDs. The incidence of serious infections and malignancies is comparable between the users of sDMARDs, TNF-inhibitors and rituximab. Compared to sDMARD users, bDMARD users had a higher incidence of joint replacement operations while the durability of the prostheses and the incidence of post-operational infections were similar.

1 INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune disease with a prevalence of 0.8 per cent in Finland [1,2]. Symptoms comprise polyarticular joint tenderness and swelling especially in hands and feet, resulting in impaired mobility, bone erosions and progressive joint destruction due to the synovial inflammatory process [3]. Women are affected more often than men and typically first symptoms arise in persons over 50 years of age, two-thirds of whom are at working age at the time of diagnosis [2,4]. Currently diagnosis of disease relies on the ACR/EULAR classification criteria of 2010 that may help identifying patients that are most likely to benefit from early initiation of therapy [5]. Several clinical, laboratory and patient self-reported measures are being used to quantify the severity of RA such as the number of swollen and tender joints, C-reactive protein (CRP) level and health assessment questionnaire (HAQ).

Treatment of RA is focused on reducing the inflammatory process and retaining the patients' physical ability always aiming at remission or low disease activity using a treat-to-target approach [6,7]. European guidelines suggest starting Disease Modifying Anti-Rheumatic Drug (DMARD) therapy using a synthetic DMARD (sDMARD) strategy in combination with glucocorticoids, followed by the addition of a biological DMARD (bDMARD) or another cDMARD strategy if the treatment target is not reached within 6 months (or improvement not seen at 3 months) [8]. In Finland, current care guidelines suggest that early RA should be treated with methotrexate (MTX) or in more severe cases with a combination of MTX, hydroxychloroquine, sulfasalazine and prednisolone [7,9].

Synthetic DMARDs are small-molecule drugs, which have been used in treatment of inflammatory diseases for several decades and comprise drugs such as MTX, SSZ, HCQ, leflunomide and intra-muscular gold. The first biological drug was introduced to clinical use in 1999. Biological drugs are currently recommended for patients with insufficient treatment response or intolerance to sDMARDs including MTX [7]. In case of treatment failure with the first biological treatment, usually tumour necrosis factor (TNF)-inhibitors, any other biological drug may be considered. At the moment, nine different biological drugs (infliximab, etanercept, adalimumab, anakinra, rituximab, abatacept, tocilizumab, certolizumab pegol and golimumab) have been authorized for the treatment of RA in Europe [10]. In addition, two biosimilar alternatives for infliximab were authorized in 2013. The number of patients using self-administered biologic drugs and the ensuing medication costs more than quadrupled between 2004 and 2012 ([11], personal communication Saastamoinen Leena/KELA September 2009). No information on the use of intravenously administered biologics is available from administrative databases.

Moreover, it is not known to what extent non-biologic sDMARDs are used concomitantly with biologic treatments.

Majority of the information on the efficacy and safety of biologic treatments has been derived from randomized controlled trials (RCTs), which are required by the medicines agencies before a drug gains marketing authorization. While RCTs can provide high quality evidence their stringent inclusion criteria for patients and often brief follow-up times limit the generalizability of the results to routine care [12]. Observational trials based on either retrospective, administrative healthcare data or purpose-collected prospective data can provide results based on the true use of medicines among real patients [13]. Furthermore, observational trials often comprise large number of patients, enabling the researchers to study correlations between the use of medication and outcomes with low incidence. However, observational trials are prone to various types of biases, which reflect the lack of randomization and the quality and completeness of the data.

RCTs have shown that biologic drugs in combination with sDMARDs reduce patients' symptoms better than sDMARDs although the main active comparator used in most trials usually has only been methotrexate as monotherapy. In early disease, the few studies having featured a combination of sDMARDs as an active comparator, have demonstrated a more modest improvement in terms of efficacy, or none at all [14–16]. Nevertheless, initiating a TNF-inhibitor early in the course of the disease may help to inhibit or delay radiological progression compared to any non-biological treatment as also stated in current therapy guide lines. It is assumed that the delayed radiological progression decreases the need for joint replacement surgery. However, aside from reduced overall incidence of joint replacement operations among RA patients, little actual evidence is available to support that conclusion [17,18]. Only a handful of RCTs have compared biologic drugs to one another [19,20]. In the absence of more head-to-head studies, systematic reviews featuring a meta-analysis can provide some evidence on the comparative effectiveness and safety of individual biologic agents [21,22].

Numerous RCTs have shown that biologic drugs have a safety profile comparable to methotrexate with some differences, most notably the increased risk for tuberculosis reactivation [22,23]. Observational studies however, have identified an increased incidence for several types of infections and malignancies among users of TNF-inhibitors compared to sDMARD users although the evidence available thus far may be insufficient to conform the causality [24].

2 REVIEW OF THE LITERATURE

2.1 Rheumatoid arthritis

2.1.1 Incidence and prevalence

Rheumatoid Arthritis (RA) is a chronic autoimmune disease, which is divided into seropositive and seronegative subtypes based on the presence of Rheumatoid Factor (RF) and Anti-Cyclic Citrullinated Peptide (Anti-CCP) [3]. Prevalence of RA in Northern Europe ranges from 0.5 to 1.0 per cent of the population while 0.8% of Finnish people have been diagnosed with RA [1,25]. The prevalence in the Northern America resembles that of Northern Europe although as much as six per cent of Native Americans may be affected whereas the prevalence is considerably lower in southern Europe and Asia. The annual incidence of RA in Finland has been estimated to be 26.7/100 000 persons and has been declining during the past decades [26]. The mean age at the diagnosis of RA is close to 60 and it is more common among women compared to men [3,26].

2.1.2 Symptoms

The most important symptom of RA is joint inflammation, which causes tenderness and pain, morning stiffness and restriction of mobility [3]. The typical joint involvement early in the course of the disease is swelling of the proximal interphalangeal joints, the metacarpophalangeal joints, the wrists and the metatarsophalangeal joints. Although the symptoms often arise from small and medium joints symmetrically on both sides, the disease can also start with monoarthritis, for example, of the knee and later develop into a more polyarticular, and classically symmetrical disease. The symptoms may also comprise fever and extra-articular manifestations such as pericarditis, pleuritis, sicca syndrome, nodules and interstitial lung fibrosis. Moreover, patient may feel fatigued. Over time, the chronic nature of RA may lead to physical disability.

2.1.3 Diagnostic procedures

RA is diagnosed by a combination of clinical findings and laboratory tests and several diagnostic criteria have been published, including the American College of Rheumatology (ACR) 1987 criteria [3,7,27]. Although the usefulness of the ACR 1987 criteria in clinical routine have been questioned, they are highly specific distinguishing RA from other rheumatic diseases in randomized clinical trials. Newer criteria, aiming specifically at identifying early RA were published in collaboration between the ACR and European League against Rheumatism (EULAR) in 2010 [5]. The ACR/EULAR 2010 criteria comprise four individually scored dimensions, namely joint involvement, serology, acute-phase

reactants and duration of symptoms (Table 1). Patients accumulating a total score of six or more out of ten are classifiable as having RA.

Table 1. Scoring table for ACR/EULAR 2010 classification criteria for Rheumatoid Arthritis [5].

Dimension	Condition	Score
Joint involvement	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joint	3
	>10 joints (at least one small joint)	5
Serology	Negative RF and negative anti-CCP	0
	Low positive RF or low positive anti-CCP	2
	High positive RF or high positive anti-CCP	3
Acute phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	Less than 6 weeks	0
	More than 6 weeks	1

RF=Rheumatoid factor; Anti-CCP= Anti-Cyclic Citrullinated Peptide; CRP=C-Reactive Protein; ESR=Erythrocyte Sedimentation Rate

Typical findings of joint inflammation comprise soft tissue swelling and tenderness, limited motion and synovitis [3,7]. Routine laboratory tests include C-reactive protein (CRP) concentration and erythrocyte sedimentation rate (ESR) as well as tests for RF and anti-CCP antibodies. Additionally, thrombocytosis, leukocytosis and reduced hemoglobin may also be present in active inflammatory disease. Furthermore, it is recommended to perform a general laboratory screening to examine any abnormalities in liver or kidney function. Imaging procedures typically used for RA patients comprise ultrasonography, x-ray imaging and magnetic resonance imaging. Ultrasonography may be used to detect swelling of the synovial membrane, or synovitis of involved joints. Also, a trained examiner can detect erosions of smaller joints at an early stage using ultrasound. While joint erosions examined using x-ray imaging is still the gold standard for diagnosing joint damage, the absence of erosions does not exclude the possibility of RA. The x-ray images of hand and feet are often evaluated at disease onset and subsequent evaluations at one and two years are used to assess disease progression [7].

2.1.4 Long-term outcomes

Rheumatic joints may be eroded to a point that either the pain or limited mobility warrants replacing the joint with prosthesis. In 2011, more than 20,000 hip and knee total joint replacements were performed in Finland, which is nearly 80% increase from year 2000 [28]. However, recent evidence suggests that the growth in the need for joint replacement operations is not due to RA, but osteoarthritis (OA) [29,30]. Estimated 25% of RA population will undergo a total hip replacement (THR) or a total knee replacement (TKR) operation within 21.8 years of the disease onset [31]. In addition, traditional rheumatic surgery comprises operations such as non-total joint replacement operations of minor joints and the removal of inflamed joint tissue (synovectomy). However, recent literature suggests that the need for rheumatic surgery, including total joints replacements (TJR) has been on the decline during the past decade [17,18,32–35]. In California, the incidence rate of THR was reduced from 363 operations per 100,000 person-years (CI 95% 352 to 375) in 1998-2002 to 324 (95% CI 313 to 334) in 2003-2007. Concomitantly, the rates of wrist and ankle operations decreased while the rates of TKR ascended [33]. Similarly in Sweden, the incidence rate of THR decreased from 12.6 operations per 1,000 person-years in 1998-2001 to 4.8 in 2002-2006 while the rates of TKR slightly elevated [18].

Studies from different countries have shown that within three years of disease onset, up to 37% of previously employed patients with RA have become work disabled [36]. Although recent trends in Finland suggest a decreased incidence of work disability pension due to RA, the standardized incidence rate ratio is nevertheless three-fold compared to general population [37].

2.1.5 Pathogenesis of rheumatoid arthritis

The pathogenesis of RA is complex, heterogeneous and to some extent, still unknown [38,39]. In essence, the body's own defense mechanisms, which are programmed to defend the host from external threats, cause unintended excessive inflammation in the synovial joints. The immunological process that eventually leads to clinical symptoms is due to a complex interplay between the innate and adaptive immune systems, central nervous system and hypothalamus-pituitary-adrenal axis. Autoantigens and corresponding autoantibodies may be formed already in the subclinical phase of RA [40]. Homozygotic twins have a higher risk for RA in comparison to heterozygotic twins given that the other twin already has been diagnosed with the disease and heritability is estimated to be 50-60% [41]. In addition to genetic factors, environmental factors such as

smoking, air pollutants, viral or bacterial agents and heavy coffee consumption may also predispose to rheumatoid arthritis [41–44]. Gonadal and adrenal hormones also play a role, which is highlighted by the sexual disparity in the incidence of RA and the fact that pregnancy may suppress the disease activity [45,46]. Progesterone and 17β-oestradiol at ovulatory to pregnancy levels stimulate B-cells while simultaneously inhibiting T-cells and macrophages and therefore women between puberty and menopause are more likely to suffer from B-cell driven RA rather than T-cell driven RA as is speculated to be the case with men and older women [38,46].

Tissue damage is mediated through both innate and adaptive immune systems [38]. After being presented an antigen by professional antigen presenting cells, activated Th1 and Th17 helper T-cells migrate to the synovial membrane to both inflict direct cellular damage through oxidative stress and to amplify the inflammatory reaction by means of releasing pro-inflammatory cytokines such as TNF, interleukin 1 (IL-1) and interleukin 6 (IL-6), interleukin 17 (IL-17) as well as adhesion molecules, matrix metalloproteinases (MMPs) and also receptor activator of nuclear factor kappa-B ligand (RANKKL) [47] . Like T-cells, also B-cells are activated by contact with innate immune cells and contribute to the inflammatory process by producing antibodies such as RF and anti-CCP antibodies. Of the innate immunity cells, macrophages have a central role in the arthritic inflammation. Local synovial inflammation might lead to formation of citrullinated fibrinogen and thereafter, generation of anti CCP-antibodies and immune complexes, amplifying the synovitis process. The changes in the balance of the immune system lead to several interconnected pathophysiological consequences: synovial hyperplasia, angiogenesis, attraction and accumulation of immune cells to the synovium, spreading of inflamed synovial tissue and destruction of articular cartilage, bone and periarticular soft tissues and subsequently bone [39].

2.2 Measures of disease activity and treatment response in Rheumatoid Arthritis

Disease-activity measures used in clinical trials of RA comprise a variety of different measures; clinical outcomes, laboratory tests and patient reported outcomes (PRO) typically reflecting the symptoms and clinical features of the condition [48]. The most frequently used clinical outcomes are the number of tender and swollen joints (TJC/SJC) based on scales typically measured using either 28 or 66/68 joint counts and the physicians evaluation of global disease activity [49–51]. Laboratory tests focus on acute-phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Additionally, the PROs comprise a measure of physical function and the patients' evaluation of global disease activity and pain, often using a visual analogue scale (VAS).

VAS usually features a 100mm horizontal line, where 0mm represents the minimal and 100mm the maximal quantity of the symptom to be measured. Physical function is commonly evaluated using the Health Assessment Questionnaire Disability Index (HAQ-DI), which is a modification from a more comprehensive questionnaire [52–54]. HAQ-DI comprises eight dimensions each with two or three questions. Answers to the questions are scored from 0 to 3, higher value signifying worse physical function. Additionally, the use of aids and devices as well as the need for outside help is inquired and used to adjust the score of related questions. Each dimension is assigned the highest score of its questions while the total HAQ-DI score is equal to the mean score of all dimensions.

To simplify the interpretation of different individual disease activity measures various indices have been developed. Disease Activity Score based on the 28-joint count includes four variables, namely the number of tender and swollen joints, CRP or ESR and the patients global assessment of general health [49]. The formulae for DAS28 (ESR) and DAS28 (CRP) are presented in the Formula 1. Patient can be considered to be in the state of remission or low disease activity if the DAS28 score is lower than 2.6 or 3.2, respectively [50] (Table 1). A score between 3.2 and 5.1 signifies moderate disease activity while severe disease activity is defined as having a DAS28 greater than 5.1. Other indices comprise Simplified Disease Activity Index (SDAI) consisting of 28-joints counts, patient's evaluation of general health, physician's evaluation of general health and the CRP-level and Clinical Disease Activity Index (CDAI), which features same variables as the SDAI except the CRP [50,55,56]. The formulae for SDAI and CDAI are presented in Formula 1.

Formula 1. Formulae for disease activity indices

$$DAS28\ (ESR) = 0.56 * \sqrt{TJC28} + 0.28 * \sqrt{SJC28} + 0.70 * Ln(ESR) + 0.014 * GH\_1$$

$$DAS28\ (CRP) = 0.56 * \sqrt{TJC28} + 0.28 * \sqrt{SJC28} + 0.36 * Ln(CRP\_1 + 1) + 0.014 * GH\_1 + 0.96$$

$$SDAI = SJC28 + TJC28 + GH\_2 + PGH + CRP\_2$$

$$CDAI = SJC28 + TCJ + GH\_2 + PGH$$

DAS28 = Disease Activity Index 28; SDAI = Simplified Disease Activity Index; CDAI = Clinical Disease Activity Index; TJC = Tender Joint Count based on 28 joint count; SJC = Swollen Joint Count based on 28 joint count; ESR = Erythrocyte Sedimentation Rate; GH_1= Patients assessment of general health on 0-100mm visual analoque scale; CRP_1 = C - reactive protein (mg/l); GH_2= Patients assessment of general health on 0-10 scale ; CRP_2 = C - reactive protein (mg/dl); PGH= Physicians assessment of general health on 0-10 scale

Table 1. Cut-off Values for DAS28, SDAI and CDAI composite measures

Disease Activity	*DAS28*	*SDAI*	*CDAI*
Severe/High	*>5.1*	*≥26*	*≥22*
Moderate	*≤5.1*	*<26*	*<22*
Low	*<3.2*	*<11*	*<10*
Remission	*<2.6*	*≤3.3*	*≤2.8*

DAS28 = Disease Activity Index 28; SDAI = Simplified Disease Activity Index; CDAI = Clinical Disease Activity Index;

Treatment response can be presented either as the change in DAS28 or alternatively, using the EULAR treatment response criteria, which account for the magnitude of the change as well as the disease activity at baseline [57]. Alternatively, treatment response criteria by the American College of Rheumatology (ACR) are solely based on the relative change from the baseline [58]. The criteria for improvement are as follow: 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR core set measures: patient and physician global assessments, pain, disability and an acute-phase reactant [48,58]. Similarly, as 20% improvement is required for ACR20 response, 50%, 70% and 90% improvements are required for ACR50, ACR70 and ACR90 responses, respectively.

Joint damage is typically assessed using a series of x-ray images of mainly hands and feet [50]. Scoring systems such as Larsen score and Sharp's method have been developed and validated to assess the severity of erosions, but their use is limited mainly to randomized clinical trials.

Several criteria for remission in RA have been developed. The remission criteria by ACR published in 1981 was very stringent and the authors described remission as the total absence of articular and extra-articular inflammation and immunologic activity related to RA [59]. Moreover, it included domains that are absent in the subsequent 'core-set' measures later defined by the ACR [48]. Subsequent introduction of composite measures such as DAS28 and its cut-off values representing remission proved themselves a valuable tool in clinical practice although there is some debate whether they are stringent enough [60,61]. In 2010, EULAR and ACR defined new criteria mainly to be used in clinical trials, which they described stringent but achievable [62]. The ACR/EULAR 2010 criteria feature two optional methods of defining remission, either a Boolean based definition or an index-based definition. The Boolean criteria require that the patient has no more than one tender and one swollen joint, CRP level no higher than one milligram per deciliter and the patients assessment of general health on 0-10 scale less or equal than one. Alternatively, the index-based definition is based on the SDAI requiring a composite score of less or equal than 3.3.

2.3 Treatment of Rheumatoid Arthritis

2.3.1 Treatment recommendations

Medical treatment of RA is aimed at reaching clinical remission, defined as the absence of clinical signs and symptoms of significant inflammatory disease activity [7,8]. Alternatively, among patients with long-standing disease, low disease activity may be a sufficient goal. Concurrent treatment strategy is known as Treat-to-Target approach where composite measures of disease activity are used on follow-up visits taking place every 1-3 months during active disease and treatment is adjusted at least every 3 months until the treatment aim is achieved [8].

Following a clinical diagnosis of RA, EULAR recommends starting the treatment with MTX or with a combination of synthetic DMARDs typically comprising MTX, SSZ and HCQ [8]. If the treatment target is not reached, and poor prognostic factors are present (presence of autoantibodies RF or ACPA; high disease activity measured by composite indices) addition of a bDMARD should be considered. Otherwise in the case of insufficient treatment response or contraindication to MTX, leflunomide or its combination with SSZ can be used. The first biologic is recommended to be a TNF-inhibitor, abatacept, tocilizumab or in certain conditions, rituximab. Should the treatment with first biologic be discontinued owing to lack of effectiveness or toxicity a second biologic, preferably abatacept, rituximab, tocilizumab or a second TNF-inhibitor should be commenced. The EULAR recommendation also includes the JAK-inhibitor tofacitinib even though it has not been authorized by EMA for treatment of RA.

According to the Finnish current care guidelines, treatment of RA should commence with MTX and in severe cases with the combination of MTX, SSZ HCQ and low-dose prednisolone, the so-called RACo combination [7]. In case of insufficient treatment response or intolerance to the synthetic disease modifying anti-rheumatic drugs (sDMARDs), biologic drugs, primarily TNF-inhibitors may be commenced. Should the treatment with TNF-inhibitors be unsuccessful, other biologics may be considered. The Finnish recommendations differ somewhat from the EULAR and ACR recommendations mainly due to the pivotal FIN-RACo and NEO-RACo studies [9,15].

2.3.2 Synthetic disease-modifying anti-rheumatic drugs

Synthetic Disease Modifying Anti-Rheumatic Drugs (sDMARDs) are a heterogenous group of small molecule drugs, which have a positive impact on symptoms and radiological joint damage [6]. Biochemical and pharmacokinetic properties as well as cellular targets of sDMARDs vary from agent to another. Commonly used sDMARDs comprise methotrexate

(MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), leflunomide and to a lesser extent intramuscular gold, cyclosporine and azathioprine [6,7]. Other sDMARD nowadays unavailable in Finland or considered obsolete and used to lesser extent include podophyllotoxine, auranofin and D-penicillamine. Cyclophosphamide is reserved for refractory cases not responding to other means of therapy.

MTX is a mainstay and anchor drug in the treatment of RA due to its favorable efficacy/toxicity ratio [6]. Resembling folic acid, MTX is a competitive antagonist of folate-dependent enzymes. The mechanism of action for MTX is complex however, and while folate antagonism appears to play some role, bulk of the anti-inflammatory effect is mediated by an increase in endogenous adenosine release and the consequent down regulation of neutrophils, macrophages and T-cells [6,63,64]. MTX is administered either orally or parenterally (subcutaneously or intramuscularly) once a week. Folic acid should be used concomitantly with MTX to reduce gastrointestinal, mucosal and hematological side-effects.

SSZ is a combination of sulfapyridine and 5-aminosalicylic acid, which breaks down to its components in the bowel [65]. Much like MTX, the anti-inflammatory effects of SSZ are mediated by increase in extracellular adenosine concentration [66]. An antimalarial drug nowadays used for autoimmune disorders, HCQ acts as a weak base, which allows it to enter cells and cause dysfunction in protein processing [67]. Subsequent downstream effects include reduced lymphocyte and natural killer cell activity and reduced autoantibody production. HCQ is associated with ocular toxicity in continuous use and has more modest efficacy in comparison to other sDMARDs, but is nevertheless frequently used is RA in particular in combinations with other sDMARDs. [65]. Leflunomide undergoes a rapid transformation into its active metabolite, which inhibits the synthesis of pyrimidine ribonucleotides and by doing so, the clonal expansion of activated lymphocytes [68]. Injectable gold has been used in treatment of RA for decades, but has largely been replaced by other sDMARDs with comparable efficacy, yet lesser side-effects [65]. Its mechanism of action is partially undisclosed, but known effects comprise reduced production prostaglandins, leukotrienes, IL-1 and oxygen radicals as well as down regulated proliferation of lymphocytes [65,69]. Isolated from fungus *Hypocladium inflatum gams,* Cyclosporine is used for prevention of allograft rejection in addition to being a potent anti-rheumatic agent [70]. As a calcineurin inhibitor, Cyclosporine inhibits T-cell activation and profileration by preventing transcription factors known as nuclear factor of activated T-cells (NFAT) from translocating to nucleus [71]. Like cyclosporine, azathioprine has been been used in solid organ transplantation preventing rejection. Its

mechanisms of action are diverse and comprise halting DNA replication, blocking de novo pathway of purine synthesis and interference with CD28 co-stimulation of T-cells.

Glucocorticoids are a unique class of drugs invaluable in the treatment of chronic inflammatory conditions, including RA [6]. The anti-inflammatory and immunosuppressive effects of glucocorticoids have a rapid onset and are well characterized. Prednisolone, including its prodrug prednisone is the most frequently used. Although low-dose glucocorticoids are usually well-tolerated, high dosing may lead to severe side-effects such as osteoporosis, skin fragility and infections [72]. Glucocorticoids may also be administered as intra-articular injections.

2.3.3 Biological drugs

A sentinel cytokine or "the body's fire alarm", Tumor Necrosis Factor (TNF) is thought to have beneficial effects at low concentrations such as augmentation of host defense while at high concentration it can lead to excess inflammation and organ injury [73]. The efficacy of TNF-blockade in treatment of RA was demonstrated in the 1990s using two different approaches. Infliximab, a chimeric human-murine antibody binding both soluble and membrane bound TNF was approved by United States Food and Drug Administration (FDA) in 1999, accompanied by etanercept, a genetically engineered TNF receptor 2 fused to the Fc portion of human IgG1. The effects of TNF-inhibitors fall into two categories: blockade of TNF-receptor-mediated mechanisms and induction of transmembrane-TNF-mediated mechanisms [73]. By preventing the activation of TNF-receptor by neutralizing TNF, TNF-inhibitors affect cell activation and proliferation, cytokine and chemokine production as well as ensuing cell recruitment, inflammation, immune regulation, angiogenesis and extracellular matrix degradation. Reverse signaling through transmembrane-TNF has been shown in vitro to induce cytokine suppression and endotoxin resistance, but it is unclear if such binding has functional consequences in patients. Administration of TNF-inhibitors may induce the formation of anti-drug-antibodies, which reduce the clinical effectiveness of the treatments [74]. Etanercept is an exception however, as no neutralizing anti-etanercept antibodies have been detected. To date, five TNF-inhibitors have been approved in Finland, namely infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), certolizumab pegol (Cimzia®) and golimumab (Simponi®). In 2013 European Medicines Agency (EMA) approved the first biosimilars infliximab (Remsima and Inflectra®) [75].

TNF-inhibitors aside, four other biologic drugs based on equal number of different mechanisms of action have been approved for treatment of RA. Anakinra was the third biologic drug for the treatment of RA to enter the market after infliximab and etanercept.

It is a competitive IL-1 receptor antagonist and thus down regulates IL-1 signaling. IL-1β is known to exist both locally in the RA joint and as a systemic proinflammatory cytokine [76]. Although nowadays rarely used in the treatment of RA, anakinra has found a niche in the treatment of adult-onset Still's disease and certain autoinflammatory syndromes such as cryopyrin associated periodic syndrome (CAPS) [6,77–79]. IL-6 in a pro-inflammatory cytokine contributing to host defense, and like TNF, its continuous production plays a significant role in the pathogenesis of RA [80]. Tocilizumab is a humanized monoclonal anti-body inhibiting both soluble and membrane bound forms of IL-6, which leads to effects on B-cells, T-cells, hepatocytes and various other cells. A CD20 antigen anti-body originally developed for the treatment of B cell lymphoma, rituximab induces apoptosis on CD20 positive B cells, which in turn impairs antigen presentation to T cells as well as cytokine production [81]. Rituximab is usually administered as fixed 1000mg infusions at intervals from 6 to 8 months. In addition to antigen presentation, the activation of T cells requires a second signal mediated by co-stimulatory molecules, of which CD28 may be the most important [82]. Abatacept is a fusion protein directly targeting T cells by a mechanism called 'costimulatory blockade' by binding to and blocking the CD80/86 present on the antigen-presenting cells and thus, inhibiting CD80/86 mediated stimulation of T cells via CD28 located on the surface of T cell. Consequently, cytokine production and B-cell activation are down regulated.

2.3.4 Efficacy and safety of biological drugs in randomized clinical trials

2.3.4.1 Infliximab

Studies have demonstrated that the combination of infliximab and MTX is superior in efficacy compared to MTX alone [83–85]. Maini et al. showed that 27% of the infliximab-treated (3mg/week every 8 weeks) patients reached ACR50 response at 30 weeks while the same outcome was reached by only 4% of the patients on MTX monotherapy [85]. Lipsky et al. 2000 confirmed the results by showing that while only 8 per cent of methotrexate treated patients reached ACR50 response at 54 weeks, the infliximab patients fared much better (21% to 39%) in a dose-responsive manner [84]. In a study by St Clair et al. 32.1, 45.6 and 50.4 per cent of patients reached ACR50 response at 54 weeks in MTX alone, infliximab 3mg/kg + MTX and infliximab 6mg/kg + MTX groups, respectively [83]. St Clair et al. observed a higher incidence of serious adverse events among infliximab users (11% vs. 14%) as compared to patiens on MTX only, which was not seen in the other two studies. However, the other studies detected an elevated incidence of mild infections as well [83–85].

2.3.4.2 Etanercept

Moreland et al. compared etanercept at doses of 10mg and 25mg per week to placebo and found that either dosage of etanercept was associated with statistically significantly higher proportion of patients reaching ACR50 response at six weeks [86]. In a study by Klareskog et al. ACR50 was reached by 69%, 48% and 43% of etanercept + MTX, etanercept alone and MTX alone treated patients [87,88]. Keystone et al. confirmed previous findings on efficacy and showed that etanercept can be administered once a week at dose of 50mg in addition to standard dose of 25mg twice a week. No statistically significant differences in the incidence of adverse event between etanercept and the comparator treatment, with the exception of injection site reactions were found [86–88].

2.3.4.3 Adalimumab

The ARMADA trial was set to study the efficacy and safety of adalimumab with three different dosages among patients with active RA despite the ongoing MTX treatment. ACR50 was reached by 8.1, 31.9, 55.2 and 42.5% of the patients on placebo or 20, 40 or 80mg of adalimumab every other week [89]. Similar results were obtained in a study by Keystone et al. where 9.5, 37.7 and 41.5% of patients qualified for ACR50 response at week 52 among placebo + MTX, adalimumab 20mg weekly + MTX and adalimumab 40mg weekly treated patients, respectively [90]. In patients with severe RA, adalimumab monotherapy was more efficacious as any of the four tested dosage regimens than placebo [91]. Exposure to adalimumab was not associated with greater risk for adverse events compared to placebo although mild adverse events such as headache, rash and injection site reactions occurred more frequently in the adalimumab group [89–91].

2.3.4.4 Golimumab

The results obtained by Kay et al proved the combination of golimumab and MTX to be more efficacious than MTX alone, measured by the proportion of patients reaching ACR50 response at week 16 [92]. In another study Keystone et al. confirmed these findings although by week 24 the differences between MTX and golimumab monotherapies were no longer statistically significant [93]. Emery et al. also compared golimumab monotherapy and the combination of golimumab and MTX to MTX alone and found that at week 24 there was no statistically significant difference in efficacy [94]. The safety profile of golimumab in clinical trials was comparable to MTX although nausea, injection site erythema and headache were more common among golimumab treated patients [92–94].

2.3.4.5 Certolizumab pegol

The efficacy and safety of certolizumab pegol was compared to MTX by Fleischmann et al. and the results showed that a statistically significantly greater percentage of certolizumab pegol treated patients reached ACR50 response at week 24 (22.7% vs. 3.7%) compared to ones receiving placebo [95]. Another trial comparing the combination of certolizumab pegol and MTX to MTX alone showed that certolizumab pegol is also efficacious as a combination treatment [96]. Serious adverse events including serious infections and malignancies were observed more frequently among the certolizumab pegol treated patients.

2.3.4.6 Anakinra

Early studies established Anakinra to be better than placebo both in achieving clinical response and delaying radiographic progression [97,98]. Cohen et al. compared MTX monotherapy to combination of anakinra and MTX and found that the combination therapy was associated with statistically significantly better efficacy, measured as the proportion of patients reaching ACR50 response (17%vs. 8%) [99]. Adverse events occurred more frequently in the anakinra group (90%) compared to MTX group (81%).

2.3.4.7 Rituximab

In a trial, which aimed to explore the efficacy and safety of rituximab among patients with previous unsuccessful TNF-inhibitor treatments, patients on rituximab + MTX reached ACR50 response at week 24 significantly more often (27% vs 5%) than the control group [100]. Overall, 88% of placebo treated patients reported an adverse event in comparison to 85% of the rituximab-treated patients. Similar results were obtained by Emery et al. who also found that while higher dose of rituximab (2x1000mg) was associated with similar efficacy as lower dose (2x500mg) measured as proportion of patients reaching ACR50, greater percentage of patients among high-dose group reached ACR70 response. Subsequent infusions of rituximab have been shown to maintain the clinical response [101].

2.3.4.8 Abatacept

Abatacept was proven an efficacious and safe co-therapy to MTX in a trial by Westohovens et al. [102]. The proportion of patients reaching ACR50 response at 1 year was 57.4% in abatacept + MTX group, as compared to 42.3% among patients treated with MTX alone. Safety of abatacept was favorable when admistered as a co-therapy with non-biologic DMARDs although patients with Chronic Obstructive Pulmonary Disease might be predisposed to increased rate of adverse events during abatacept treatment [103].

2.3.4.9 Tocilizumab

Tocilizumab was tested against placebo in a trial that allowed co-medication with sDMARDs, revealing that the tocilizumab-treated patients reached ACR50 response significantly more often (37.6% vs. 9.0%) than patients receiving placebo [104]. The results were similar among patients with previous unsuccessful treatments with TNF-inhibitors [105]. In a comparison between tocilizumab and MTX monotherapies, tozilizumab was associated with better outcomes although the difference was considerably more subtle than in previous comparisons [106]. Safety of tocilizumab was deemed comparable to MTX in all three trials [104–106].

2.3.4.10 General features of RCTs studying the efficacy and safety of biological drugs in RA

Numerous RCTs have addressed the efficacy and safety of biologic drugs in treatment of RA; the first publications dating back do early 1990s [107]. Vast majority of the RCTs compare the biologic drug to placebo or MTX, which do not represent the current treatment recommendations on the best synthetic treatment [8,108]. In particular from the point of view of Finnish treatment strategy, effective combinations of DMARDs should be used at appropriate doses, preferably comprising MTX, SSZ, HCQ and low-dose prednisolone. Few such studies have emerged lately, providing better generalizability to clinical practice. A Swedish non-blinded interventional trial randomized patients with unsatisfactory response to MTX alone to additionally receive either HCQ and SSZ or alternatively, infliximab. The patients receiving infliximab had a slightly better ACR50 response at 12 (25% vs. 15%) and 18 (30% vs. 19%), but at 24 months the difference was no longer statistically significant (30% vs. 22%) [109]. Meanwhile in a Finnish trial, Leirisalo-Repo et al. investigated whether the addition of infliximab to RACo combination therapy in the so called NEO-RACo study would yield improved outcomes [15]. According to the results, infliximab-treated patients were statistically non-significantly more often in remission at two years after the therapy onset (66% vs. 53%) and also non-significantly more often achieved ACR50 response.

Despite the wealth of information on biologic drugs being compared to placebo or MTX, few trials to date have compared individual biologic agents to one another [19,110]. One such study was the AMPLE trial, which compared abatacept to adalimumab among biological-naïve patients with concomitant MTX treatment and revealed that the two biologic drugs, although based on different mechanism of action, are comparable in efficacy and safety.

2.3.5 Effectiveness and adverse effects of biologic drugs in observational studies

2.3.5.1 Treatment response and drug survival

The effectiveness of biologic drugs in treatment of RA has been studied in several European countries using data from prospective cohort studies although most literature concerns only TNF-inhibitors [111–114]. Moderate and good EULAR treatment responses at six months were achieved by 67 – 85% and 17 – 52%, respectively (Table 2). In multivariate regression analyses, etanercept and adalimumab were generally associated with better treatment response compared to infliximab [111–114]. Most commonly identified predictors of treatment response were concomitant sDMARDs, especially MTX and baseline disease activity as well as smoking [111–113,115]. No difference has been observed in effectiveness of TNF-inhibitors between men and women [116]. In case of treatment failure, it has been shown that treatment with another TNF-inhibitor may be beneficial [117].

Table 2. Percentage of RA patients achieving at least moderate and good *(latter in parentheses)* EULAR response after 6 months of treatment onset.

Study	Infliximab	Etanercept	Adalimumab	Pooled TNF-inhibitors
Hyrich et al. 2006 [111]	69% (19%)	67% (17%)	-	68% (18%)
Hetland et al. 2010 [112]	71% *(34%)*	81% *(42%)*	85% *(52%)*	77% *(41%)*[1]
Canhao et al. 2012 [114]	*(33%)*	*(39%)*	*(40%)*	*(38%)*[1]
Flouri et al. 2014 [113]	69% *(20%)*	78% *(19%)*	72% *(24%)*	72% *(21%)*[1]

[1]Pooled results not reported, but calculated based on available data

In Denmark, 19% and 34% of RA patients discontinued their first TNF-inhibitor treatment within six and twelve months of treatment onset, respectively [112]. The most common reasons for discontinuation were lack of effectiveness and adverse events. In a Northern-Italy based cohort, 79%, 65% and 53% of patients remained on the treatment after 12, 24 and 36 months of treatment onset, respectively [118]. Results by Hyrich et al. show that 81% of TNF-inhibitor users remain on treatment after 6 months [111]. Adalimumab and etanercept have been associated with better drug survival as compared to infliximab [112,113].

2.3.5.2 Serious infections

Patients with RA have an increased risk for infections, possibly due to both immunosuppressive medication and the disease process itself [119]. The crude incidence rate of serious infections during exposure to TNF-inhibitors has been observed to range

from 2.6 to 5.5 events per 100 patient years (Table 3). Even though the information from RCTs has not consistently shown an increased risk for infections among patients treated with biologic drugs compared to sDMARD-treated patients, observational research has been performed to confirm the findings [120]. After adjusting for possible confounding, most observational studies have found a small and often statistically insignificant increase in the incidence of serious infections compared to sDMARDs [120–122]. A recent systematic review concluded that in the light of current evidence, biologic drugs are associated with increased risk for infections (Table 4) [24]. The risk for infections may be especially high during the first six months of treatment, possibly because the subset of patients susceptible to infections are less likely to stay on the treatment [123]. Furthermore, the incidence of certain types of serious infections has been detected to be higher among TNF-inhibitor-treated patients. TNF plays a role in defence against *Mycobacterium Tuberculosis* and the reactivation of tuberculosis is a recognized safety issue with TNF-inhibitors and is now being screened routinely before biologic therapy [7]. Dixon et al. compared the incidence of tuberculosis among TNF-inhibitor treated patients and found that etanercept was safer in that respect compared to infliximab and adalimumab [124]. Also, the risk for serious skin infections and shingles has been found to be elevated during exposure to TNF-inhibitors [125]. Cases of serious infections among Finnish RA patients using TNF-inhibitors have also been described in the literature [126]. Although less data is available for rituximab, compared to sDMARDs it does not seem to predispose patients to either infections [127]. MTX and glucocorticoids have been shown to increase the risk for serious infections when used concomitantly with TNF-inhibitors [123,128,129].

Table 3. Crude incidence rates per 100 patient years and corresponding 95% confidence intervals of serious infections during exposure to TNF-inhibitors.

Study	Infliximab	Etanercept	Adalimumab	Pooled TNF-inhibitors
Lane et al. 2011 [129]	-	-	-	3.6 *(3.2-4.0)*[1]
Komano et al. 2011 [128]	-	-	-	2.6 (1.2-4.1)
Strangfeld et al. 2011 [130]	-	-	-	4.8 (4.1-5.7)[2]
Galloway et al. 2011 [123]	4.6 (4.2-5.0)	3.8 (3.5-4.2)	4.3 (3.9-4.7)	4.2 (4.0-4.4)
Sakai et al. 2012 [131]	4.8 (3.3-6.7)	5.6 (4.1-7.4)	-	5.5 (4.4-6.8)
Van Dartel et al. 2013 [121]	3.9 (3.3-4.4)	1.7 (1.1-2.2)	2.6 (2.2-3.0)	2.6 *(2.2-3.1)*[1]

[1]Confidence intervals not reported, but calculated based on available data; [2]Data on the first year of treatment; TNF=tumor necrosis factor

Table 4. The adjusted hazard/risk ratios for infections among patients exposed to TNF-inhibitors in comparison to sDMARD users (modified from Ramiro et al. 2014 [24])

Study	Exposure	Control	Adjusted effect size (95% CI)
Grijalva et al. 2010 [132]	TNF-inhibitors	MTX	HR 1.3 (0.8-2.2)
Greenberg et al. 2010 [133]	TNF-inhibitors+MTX	MTX	HR 1.1 (1.0-1.3)
Grijalva et al. 2011 [122]	TNF-inhibitors	sDMARDs	HR 1.1 (0.9-1.2)
Lane et al. 2011 [129]	TNF-inhibitors	sDMARDs	HR 1.2 (1.0-1.5)
Komano et al. 2011 [128]	ETA/IFX	sDMARDs	RR 2.4 (1.1-5.1)
Galloway et al. 2011 [123]	TNF-inhibitors	sDMARDs	HR 1.2 (1.1-1.5)
Strangfeld et al. 2011 [130]	TNF-inhibitors	sDMARDs	HR 1.8 (1.2-2.7)
Sakai et al. 2012 [131]	ETA/IFX	sDMARDs	RR 2.0 (1.3-3.2)

TNF=tumor necrosis factor; MTX=methotrexate; ETA=etanercept; IFX=infliximab; sDMARD=synthetic disease-modifying anti-rheumatic drug; HR=hazard ratio; RR=risk ratio; CI=confidence interval

2.3.5.3 Malignancies

Due to the role of TNF in host defence, it was hypothesized that its blockade might lead to increased risk of malignancies, including lymphomas [134]. Controversially, increased TNF-levels have also been associated with increased risk for certain types of malignancies. Between the introduction of biologic drugs to US market in 1998 and 2000, 26 cases of lymphomas were reported to the FDA, rising concerns of the serious adverse effects [135]. The association between elevated disease activity and excessive inflammation and increased risk of lymphomas, leukaemia and myelomas has made definite causal conclusions difficult [136–138]. The incidence rates per 100 patient years of solid cancers, lymphomas or leukemias and nonmelanoma skin cancers among RA patients using TNF-inhibitors has been observed to be 0.91, 0.13 and 0.31, respectively [139]. Current evidence does identify discrete types haematological malignancies and skin tumours that may be affected by the exposure to TNF-inhibitors, but the overall risk is not increased (Table 5) [24,126,136,140–142]. It is unclear if patients with history of previous malignancy should be treated differently [24]. In Finland, TNF-inhibitors are avoided in patients with previous malignancy, nevertheless [7].

Table 5. The adjusted hazard/risk ratios for all types of malignancies among patients exposed to TNF-inhibitors in comparison to sDMARD users (modified from Ramiro et al. 2014 [24])

Study	Exposure	Control	Effect size (adjusted)
Askling et al. 2009 [142]	TNF-inhibitors	sDMARDs	HR 1.0 (95% CI 0.7-1.4)
Strangfeld et al. 2010 [143]	TNF-inhibitors	sDMARDs	HR 0.7 (95% CI 0.4-1.1)
Carmona et al. 2011 [144]	TNF-inhibitors	sDMARDs	HR 0.5 (95% CI 0.1-2.5)
Haynes et al. 2013 [139]	TNF-inhibitors	sDMARDs	HR 0.8 (95% CI 0.6-1.1)

TNF=tumor necrosis factor; sDMARD=synthetic disease-modifying anti-rheumatic drug; HR=hazard ratio; RR=risk ratio; CI=confidence interval

2.3.5.4 Joint replacement surgery

Recent Finnish study by Jämsen et al. found a trend between the increased use of sDMARDs and biologics and reduced need for joint replacement surgery in RA during the years 1995-2010 [35]. Similar trends have been observed elsewhere as well [17,34]. Regardless, another Finnish study was not able to show causality between the intensified therapy and then need for large joint replacement surgery [145]. Presently, there is insufficient information to conclude to what extent the introduction of biologic treatments has affected the need for joint replacement surgery and what can be explained with other factors.

DMARDs as well as biologic drugs aim to control the inflammation thus preventing the joint damage and premature need for joint replacement, however, especially biologic drugs have been suspected to predispose to periprosthetic infections [146–148]. Patients with RA exhibit a distinct cellular response to wear particles from artificial joints, which can lead to aseptic loosening of the prosthesis [149]. This process may be however, be mitigated by TNF-inhibitor treatment. A review article published in 2007 recommended performing elective surgery before initiating biologic treatment while more recent guidelines advice withholding biologic treatment one week before and after the operation [150,151]. It remained uncertain whether sulfasalazine and leflunomide should be discontinued before surgery, whereas methotrexate and hydroxychloroquine were considered safer. In the study by Bongartz et al. perioperative discontinuation of DMARDs and biologics did not statistically significantly reduce the risk of infection [146].

2.3.5 Usage and costs of biological drugs in Finland

The first biologic drugs available for treatment of RA in Finland were infliximab and etanercept, which were authorized throughout European Union in 1999 and 2000, respectively [152,153]. During the years 1999-2002 infliximab was the drug of choice ([154], personal communication Voipio Tiina/FIMEA October 2012) (Figure 1). Starting from 2003, etanercept and adalimumab were reimbursed by the Social Insurance Institution of Finland (KELA), which made them affordable to the patients and therefore, not influencing the hospital budgets. Consequently, majority of new biologic treatments were started using either one of the self-administered drugs instead of the intravenously administered infliximab. The use of biologic drugs other than infliximab, etanercept and adalimumab has been growing since, but was nevertheless marginal compared to the three aforementioned in 2012. In 2012, the total usage of biologic drugs was 1.85 Daily Defined Doses (DDD) per 1000 persons per day. Based on these numbers, estimated 0.19% of Finnish people or 10 300 persons were continuously using biologic drugs in 2012. On the other hand, the KELA records reveal that 7 823 people received co-payments from self-administered biologic drugs in 2012 ([11], personal communication Saastamoinen Leena/KELA September 2009) (Figure 2). The total medical costs of self-administered biologic drugs in 2012 were 97 M€, or 5.4% of all outpatient medical costs combined. Both the annual number of patients treated with self-administered TNF-inhibitors and the corresponding costs have grown more than ten-fold during a period of ten years. Altogether, 3.8 million people received co-payments from KELA in 2012 meaning that the medical costs of an average biologic drug user exceeds the population average by 27-times, not including other medications the biologic drugs user might have.

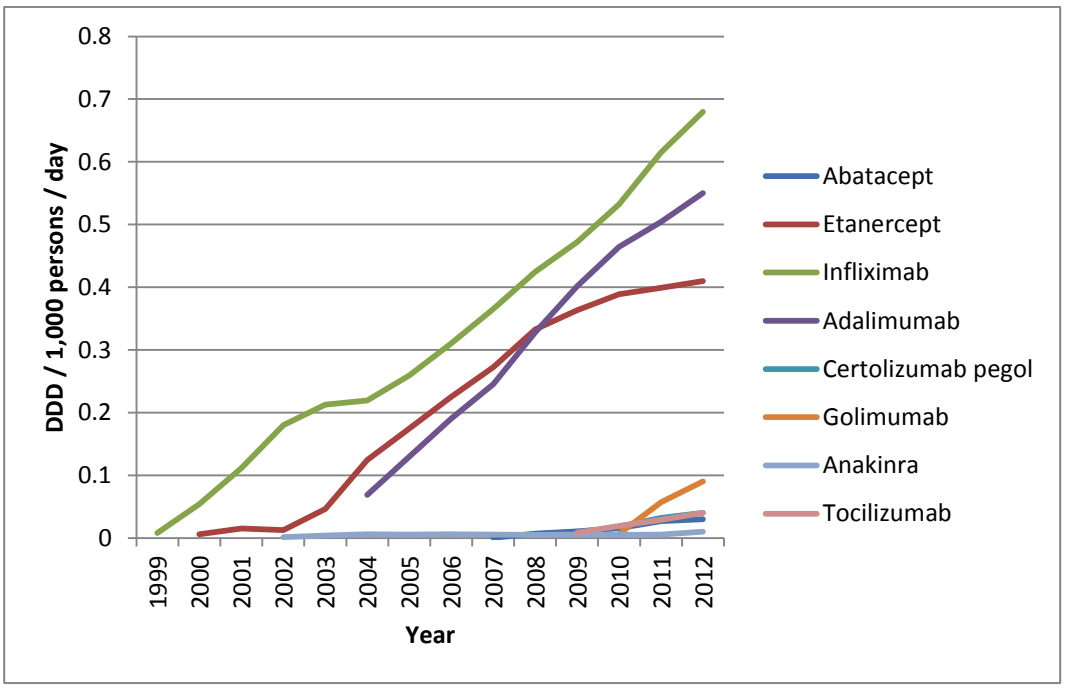

Figure 1. Use of biological therapies in Finland in 1999-2012 ([154], personal communication Voipio Tiina/FIMEA October 2012)

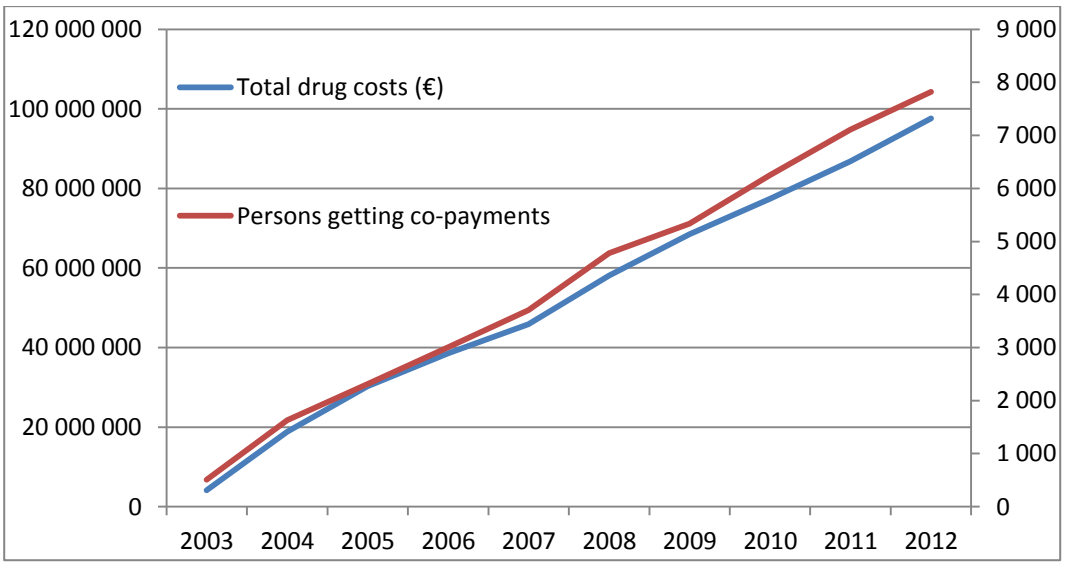

Figure 2. Social Insurance Institution of Finland (KELA) records on the number of users and total costs of biologic drug users in Finland 2003-2012 ([11], personal communication Saastamoinen Leena/KELA September 2009).

3 AIMS OF THE STUDY

1. To identify, evaluate and summarize relevant published data on TNF-blockers in the treatment of RA and to perform an indirect comparison between the drugs (Study I).

2. To perform a cross-sectional overview on demographics, disease activity and medication of RA patients in Finland (Study II).

3. To investigate the incidence of serious infections and malignancies among RA patients treated with sDMARDs, TNF-inhibitors or rituximab (Study III).

4. To assess the effectiveness of biologic drugs on the incidence of joint replacement surgery and its outcomes in comparison DMARDs (Study IV).

4 MATERIALS AND METHODS

4.1 Systematic review (I)

According to inclusion criteria patients had to be at least 16 years of age; be diagnosed with RA using ACR 1987 criteria; and be randomized either to intervention or control group. Studies were to have one (or more) of the TNF-inhibitors (infliximab, etanercept, adalimumab, certolizumab pegol or golimumab) as intervention and either placebo or combination of placebo and methotrexate as control. The included studies were to report on efficacy in terms of ACR response and safety.

Search designed by a librarian comprised the terms rheumatoid arthritis, anti-TNF, infliximab, etanercept, adalimumab, golimumab, certolizumab pegol, randomized clinical trials and systematic review. Detailed search strategy for (Ovid) Medline is available as Appendix 1. References identified from (Ovid) Medline, Cochrane library (Cochrane Central register of Controlled Trials, Cochrane Database for Systematic Reviews, Health Technology Assessment, Database of Abstracts of Reviews of Effects, NHS Economic Evaluation, Cochrane Methodology Register), SCOPUS (including Embase), ISI web of knowledge imported to reference management software (RefWorks) and duplicate entries were removed using an automated feature. There were no restrictions on study language.

References were evaluated by two individual investigators using pre-defined inclusion criteria. Decision for inclusion was made on consensus or by a third investigator (YTK) in case of disagreement. Evaluation was based on title and abstract of the reference whenever available. Full text articles from potentially relevant references were obtained in electronic or printed format and re-evaluated for inclusion by the same investigators as before. The acronym PICOS (patients, interventions, comparators, outcomes and settings) was used to assess if the references fully complied with the inclusion criteria. Multiple reports from a single study were considered as one study.

Studies included were evaluated for an eventual bias using methods described in the Cochrane handbook by two independent assessors [155]. The effect of possible bias on results was studied by performing all meta-analyses twice with possibly biased RCTs included and excluded.

Data on study design, patient status and background, efficacy and safety were extracted from the publications using an Excel data extraction form by two independent

researchers. Whenever results of a single study were reported in multiple publications, all available data was acquired and merged.

Data were analyzed using the intention to treat results from the included studies and pooled with Cochrane Collaboration Review Manager 5.0 software. Sensitivity analyses were employed to account for the possible bias. Efficacy and safety were analyzed using dichotomous data to obtain risk ratios. Dichotomous efficacy data included ACR 20%, 50% and 70% improvements whereas dichotomous safety data was composed of the proportion of patients who experienced an adverse outcome or discontinued the treatment due to adverse events. Heterogeneity was evaluated via subgroup analysis using Chi square and I^2-statistics and random effects model was used to account for the diversity of the studies [155].

4.2 Cross-sectional study (II)

Inclusion to the (Reuman Aktiivisuuden MIttaaminen) RAMI cross-sectional study was limited to RA patients diagnosed either according to the ACR 1987 inclusion criteria or alternatively, as a clinical diagnosis [27]. Additionally, patients had to be at least 16 years of age and be treated within the specialized outpatient healthcare. The study was a cross-sectional in nature and thus data was collected from a single time point. The participating rheumatology clinics were to enroll consecutive patients until the planned study size of 1000 patients was reached. The data to be collected comprised information on demographic, disease activity and medication –related variables and was collected using a pre-designed data collection form, which was divided to two sections to be filled by rheumatologist and patient. Alternatively, the data could be collected using an electronic patient monitoring software (GoTreatIt; DiaGraph, Kristiansand Norway). Afterwards, data from forms were imported into an electronic database (Access 2010, Microsoft Redmond) and merged with the electronically collected data.

Patient self-report comprised information on educational background and current employment status along with data on sick leaves, pension and work disability as well as current smoking status. The number of joint replacement surgeries was also inquired as they are not reliably recorded in the hospital records. Furthermore, the patient self-report comprised visual analogue scales for pain and global assessment along with Health assessment questionnaire disability index (HAQ-DI). Basic education was defined as either having only completed high school, vocational school or less; equaling as up to twelve years of education.

Disease activity score based on 28-joint count (DAS28), simplified disease activity index (SDAI), clinical disease activity index (CDAI) and fulfillment of ACR/EULAR 2011 remission criteria were calculated in data analysis based on their respective formulas. Descriptive data are presented either as means and medians with interquartile range (IQR) or percentages. The data were analyzed in SPSS 20 (IBM, Armonk New York) using either parametric or non-parametric tests, depending on the distribution. Percentages were calculated with and without missing cases to estimate the effect of missing data on the results; however missing data was not imputed.

Ethical statement was applied from the ethical board of each participating hospital district. Written consent was obtained from each enrolled patient.

4.3 Cohort studies (III and IV)

The study population was identified from the national register for biologic treatment in rheumatic diseases (ROB-FIN) and the hospital records of Central Finland Central Hospital with the latter providing all sDMARD users. A prospective cohort study designed to monitor the effectiveness and safety of biologic drugs in treatment of rheumatic diseases and based on structured data collection forms submitted by rheumatologists on patients' routine care visits to outpatient specialized healthcare; ROB-FIN has follow-up data dating back to year 1999. Reporting is instructed to occur at the baseline of the biologic treatment, 3 and 6 months after the treatment onset and semiannually thereafter. The electronic hospital records collected using GoTreatIT patient monitoring software were retrieved from 2007 onwards. Additionally, survey-based data forming a time-series on RA patients treated in Central Finland Hospital district 1998-2006 was used to extend the sDMARD follow-up for the analysis of joint replacement operations (IV) [156].

To be included in the cohort studies, patients had to have a confirmed diagnosis of RA (either meeting the ACR 1987 criteria or a clinical diagnosis) and had at least one recorded visit during the exposure to either biologic or synthetic DMARDs [27]. Additional inclusion criteria for the analysis of serious infections and malignancies (III) were treatment onset prior to December 31 2011 and treatment with either infliximab, etanercept, adalimumab or rituximab. Additionally, only biologic-naïve sDMARD users were included. The patient could contribute to several medication groups as long as it did not violate the inclusion criteria. The inclusion criteria for the analysis of joint replacement surgery (IV) considered all biologic and synthetic DMARD users having commenced their treatment prior to November 9th 2010 were included and accumulated at least two recorded visits eligible for the study.

Follow-up time for the study on serious infections (III) was defined either as the reported medication start and stop date, or alternatively in the absence of this information, as the time between the first and the last visit while on drug. Additionally, a six month lag-time was introduced to capture the adverse events taking place soon after the discontinuation of the exposure. However, the follow-up was truncated at the initiation of another biologic treatment or at December 31 2011. Baseline visit was defined as the first visit during the exposure or at most three months before the treatment onset unless the patient was on another biologic treatment. For the analysis of joint replacements (IV), follow-up period was defined as the time between the first and the last recorded visit while on biologic treatment. No lag-time was employed and the follow-up was truncated at November 9th 2010.

Data on study endpoints, serious infections, malignancies and joint replacement operations were acquired from National Hospital Discharge Register (HILMO), National Cancer Registry and the Implant registry, respectively [157–159]. Data on infections, malignancies and joint replacement operations were available to us from 1998 to 2011, 1953 to 2011 and 1980 to 2010, respectively. No evaluations of causality between the exposure and outcome were made; instead all outcomes occurring during the follow-up period were included. Post-operative infections were excluded from the analysis of serious infections in study (III), but included in study (IV).

The results are reported as medians with interquartile ranges (IQR), counts, incidence rates and incidence rate ratios (IRR). The 95% confidence intervals (95% CI) for IRs were retrieved from Poisson distribution based on the crude rates. Baseline differences between the groups were analyzed using analysis of variance, chi-squared test, Kruskal-Wallis or Mann-Whitney's U-test test, as appropriate. In the analysis of serious infections and malignancies (III), the IRRs were modelled using Poisson regression with adjustement for overdispersion accompanied by robust standard errors where appropriate. A full model where all observed and potentially relevant confounders were included was used. Multiple imputation (MI) with predictive mean matching and 20 imputed datasets was used to create the imputed data, which involved three steps [160]. First, several slightly different dataset were created. Second, the regression analyses were performed separately in each. And third, the correlation coefficients and standard errors were pooled together. In the analysis of joint replacements (IV) patients were matched using propensity score estimated via logistic regression, facilitating the comparison of the results of the matched patients without further use of regression analyses [161]. Kapplan-Meier survival analyses were used for the life-time analysis of joint replacement operations with log-rank tests for subgroup differences. Data were analyzed using PASW 18.02 statistical data package (IBM, Armonk, NY), SPSS 22.0 statistical data package (IBM, Armonk, NY) and R statistical programming language version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

An ethical consent for the study was granted by the ethical board of the Division of Internal Medicine at Helsinki University Central Hospital (HUCH), while the study approval was acquired from the National Institute for Health and Welfare (THL). Additionally, all patients enrolled to ROB-FIN had given their informed consent. Data from different sources were merged on a patient level using unique social security numbers and anonymized to conceal the patient identity.

5 RESULTS

5.1 Systematic review (I)

5.1.1 Literature search and study selection

Altogether, 5308 references of which 1623 were excluded as duplicates, were identified from electronic databases by a systematic literature search performed in February 2010. Additionally, 146 references were added via "search alerts", which extended time coverage of the search to 30.6.2010. No additional references were identified from alternative sources including clinical trial registers. Seventy six potentially relevant references were re-evaluated based on full text. Full text was unavailable for 12 studies most of which were conference abstracts identified from ISI Web of Knowledge [107,162–172]. Patients, interventions, controls, outcomes or design of the studies did not meet the inclusion criteria of the systematic review in 17 publications [173–189]. Five review articles, one letter to the editor [190] and one erratum [191] were excluded. Several of the remaining 41 publications were reporting on a single study and were thus merged into one [19,83–92,94–96,192–217]. From the 26 clinical trials included in the systematic review, adalimumab was used in 8, etanercept in 7 , infliximab in 5, golimumab in 3 and 3 certolizumab pegol in 3 for intervention. A flowchart of the study selection process is presented in Figure 3. The included trials have 9862 patients of which 6780 and 3082 were in intervention and control groups, respectively (Appendix 2).

5.1.2 Evaluation for bias

A potential source of bias was discovered in five trials included in the systematic review. In many clinical trials there was an early escape route for patients with insufficient treatment response to avoid rapid disease progression. In some studies this was implemented by considering all patients failing to meet a pre-defined treatment response criteria (e.g. ACR 20 % improvement) as "non-responders" before the actual efficacy assessment. While this may be for the best interest of the study subjects, it may introduce a bias to the evaluation of the efficacy results since some of these patients could have later reached treatment response.

5.1.3 Efficacy

The primary efficacy endpoint of our study was the risk ratio of 50 % improvements in the ACR-treatment response criteria at six months between intervention and control group. Fourteen trials were included and of them 2 used infliximab, 2 etanercept, 5 adalimumab, 2 golimumab and 3 certolizumab pegol for intervention. As a group, TNF-inhibitors

reached a risk ratio of 4.07 (95 % CI 2.70-6.13) regarding the achievement of the efficacy endpoint compared to controls. For infliximab, etanercept, adalimumab, golimumab and certolizumab pegol the corresponding figures were 3.08 (0.91-10.43), 8.61 (3.55-20.86), 4.34 (3.30-5.70), 1.56 (0.93-2.60) and 5.95 (3.97-8.92), respectively (Figure 4).

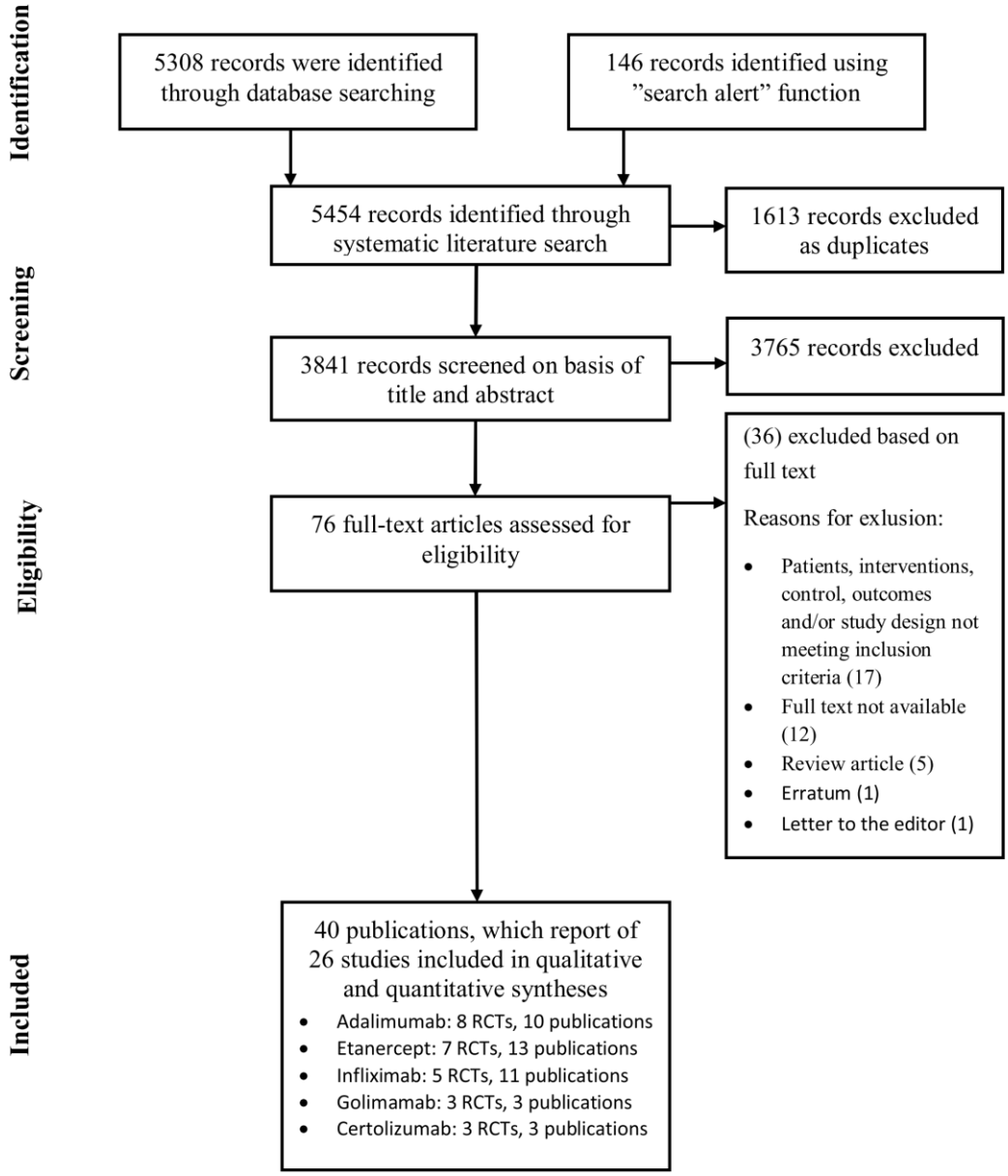

Figure 3. Flowchart of the study selection process

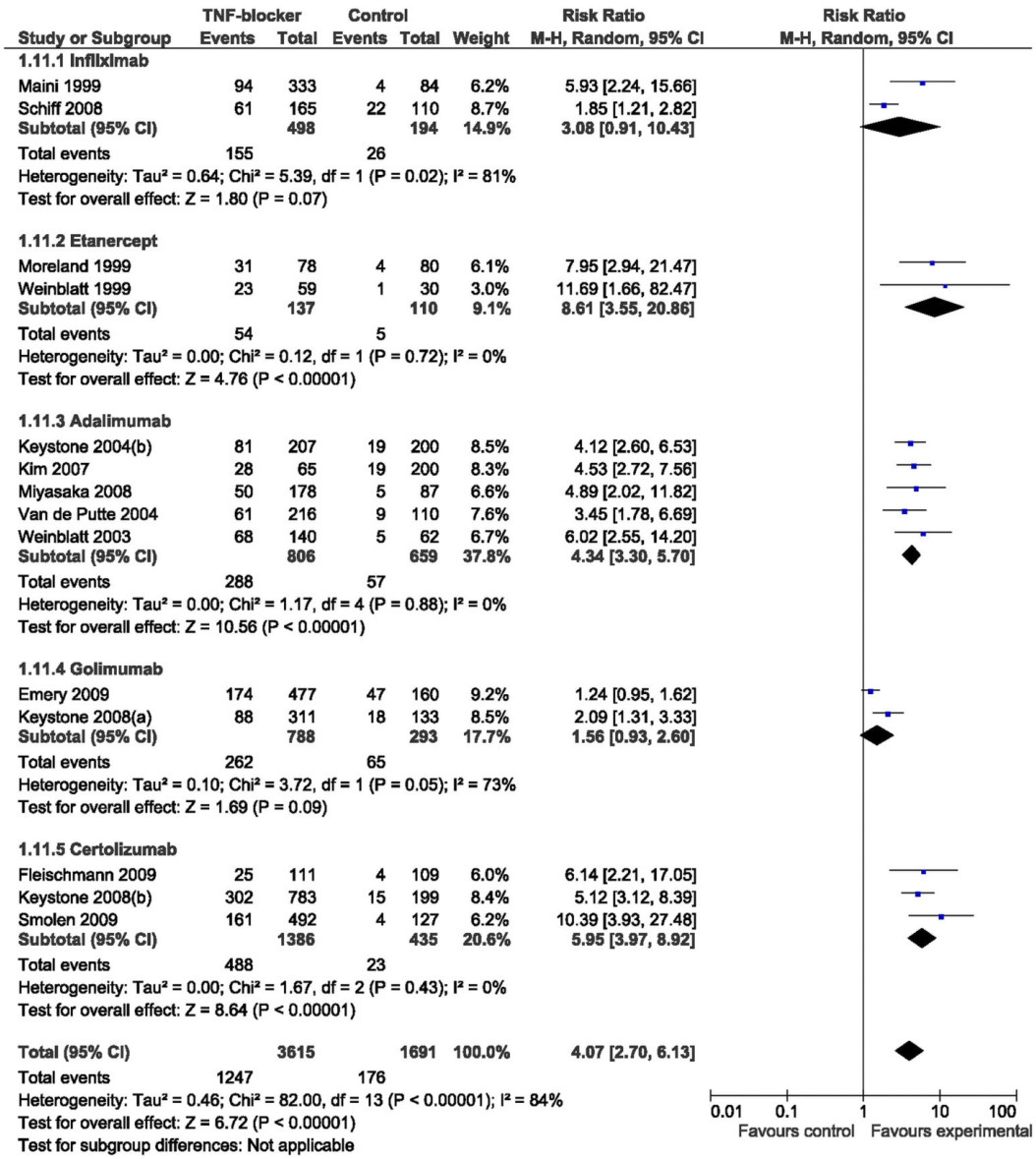

Figure 4. Forest plot of the ACR 50 response at 6 months (Aaltonen et al. 2012 [218])

Patients on combination therapy had significantly higher ACR outcomes than the ones treated with MTX alone at all time points. A statistically significant difference was revealed between ACR 20 risk ratios of certolizumab pegol (95% CI 5.08, 3.46-7.48) and golimumab (1.61, 0.94-2.76). In a sub analysis of trials in patients who had previously used MTX, the results were similar. In comparison to MTX, golimumab combination therapy was still inferior in ACR 20 efficacy at 6 months to certolizumab pegol combination therapy, with risk ratios of 2.14 (1.59-2.89) and 5.08 (3.46-7.48), respectively. At six months patients previously naïve to MTX are statistically significantly less likely to reach either ACR 20, 50 or 70 treatment responses compared to patients who had already been previously treated with MTX. The combination of TNF-inhibitor and MTX was superior in efficacy to monotherapy with a TNF-inhibitor at almost all time points. All four TNF-inhibitors were more efficacious than placebo with the estimates of risk ratios ranging from 2.74 (95% CI 1.76-4.26) – 12.31 (1.64-92.41). Increasing the dose of TNF-inhibitor provided no additional efficacy compared to regular doses except 12 months with possibly biased results excluded.

The sensitivity analyses based on the results of the bias assessments did not reveal any statistically significant bias on the efficacy results. Occasionally, however, the statistical significance between intervention and control groups disappeared due to reduced number of studies. In the sensitivity analyses, the estimate of the risk ratio decreased, increased or remained the same in 52%, 45% and 3% of cases, respectively. However, all certolizumab pegol studies were potentially biased and the effect of bias on the results could not be evaluated. Significant heterogeneity was present in the first analysis comparing any intervention to any control, but diminished as the comparisons were stratified into smaller comparisons.

5.1.4 Safety

The primary safety endpoint of the systematic review was the discontinuation of study due to adverse events. There were 25 studies with 6292 patients in the intervention and 2994 in the control group in this analysis. As a group, the TNF-inhibitors did not statistically significantly differ from the control (RR 1.26, 95% CI 0.93-1.71). While the patients on infliximab (3.22, 1.76-5.91), adalimumab (1.59, 1.13-2.23), and certolizumab pegol (2.72, 1.23-6.01), had an increased risk to discontinue, the patients on etanercept (0.71, 0.54-0.92) had a decreased risk (Figure 5). Patients using certolizumab pegol had a higher risk to experience a serious adverse event than patients on etanercept with risk ratios of 2.24 (1.38-3.63) and 0.90 (0.68-1.20), respectively. Infliximab, etanercept and golimumab increased the likelihood of an injection or infusion reaction while adalimumab and certolizumab pegol did not statistically significantly differ from the controls in this

respect. In the comparison of combination of TNF-inhibitor and MTX to MTX alone, combined results from all TNF-inhibitors reached statistical significance (1.37, 1.01-1.87). The comparison of TNF-inhibitors and placebo showed a trend of increased risk of adverse events from TNF-inhibitors, but only the increase in the frequency of injection reactions was statistically significant (RR 3.69, 95% CI 1.03-13.23). Certolizumab pegol was the only TNF-inhibitor, which increased the risk to experience an adverse event compared to placebo (1.31, 1.08-1.26). Increased dose of the TNF-inhibitors did not increase the frequency of discontinuations due to adverse events (RR 0.98, 95% CI 0.72-1.35), but the likelihood to experience an unspecified adverse event was reduced compared to normal doses (0.93, 0.89-0.97). Patients on high doses of infliximab were also less likely to suffer from infusion reactions compared to those on regular doses (0.73, 0.56-0.94).

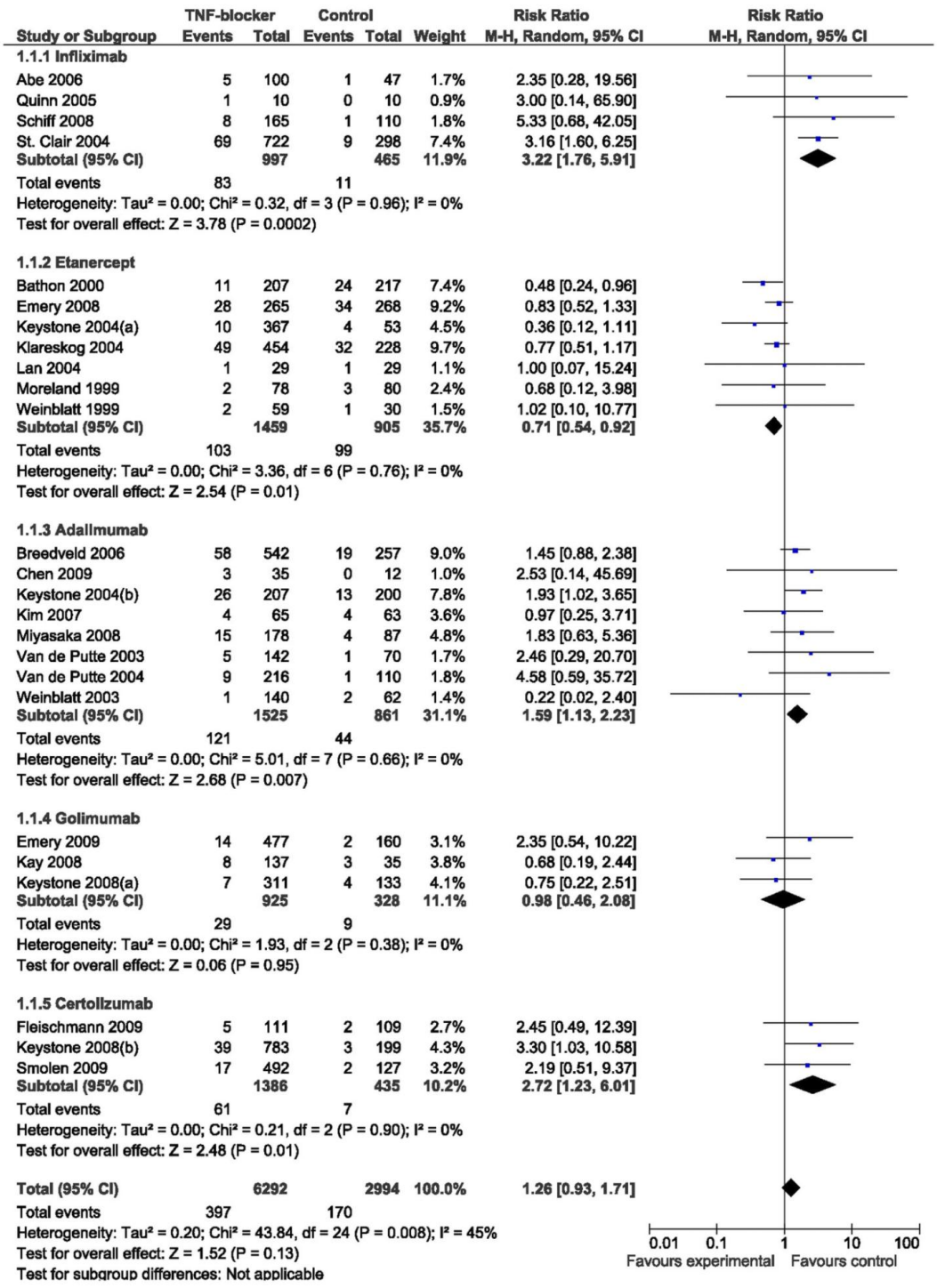

Figure 5. Forest plot of the number of discontinuations due to an adverse event. (Aaltonen et al. 2012 [218])

5.2 Cross-sectional study (II)

5.2.1 Patients and disease characteristics

Overall, 890 patients were enrolled into the study. The data collection took place between November 2011 and May 2012 in 14 sites in 6 hospital districts. Data collection paper forms were used to collect data on 76% of patients while remaining 24% were retrieved from hospital records using GoTreatIT patient monitoring software. Information on joint replacements was available from 83% of patients while all other variables had less than 10% of data missing.

Percentage of women was 77% while mean age and time from diagnosis were 58.4 (median, IQR 59.8) and 11.6 (median 7.2, IQR 3.0-17.1) years, respectively. Patients had been diagnosed with RA on average at the age of 46.4 (median 47.0, IQR 34.0-58.0). Current smokers represented 16% of total population while 95% of patients reported having at least basic education. Further information on study participants is reported in Table 6.

The mean number of tender and swollen joints were 1.61 (median 1, IQR 0-2) and 1.37 (median 0, IQR 0-2), respectively. Rheumatoid factor and anti-CCP-antibodies were evident in 70% and 63% of patients, respectively while erosions had been detected among 76%. Sixteen per cent of patients reported having undergone a large joint replacement surgery in the past. Mean HAQ-DI scores with and without aids and devices were 0.87 (median 0.75, IQR 0.13-1.4) and 0.72 (median 0.63, IQR 0.13-1.1), respectively. Disease activity as measured with DAS28 ranged from 0.28 to 6.61 (median 2.55) with 52% and 70% of patients reaching remission and low disease activity, respectively while according to the ACR/EULAR 2011 remission criteria the proportions of patients in remission were 26% (Boolean) and 28% (SDAI).

Table 6. Patient characteristics[1] (adapted from Aaltonen et al. 2014 [219])

	All patients	Women	Men
N	890	688 (77%)	202 (23%)
Age	59.8 (49.6-68.1)	59.0 (48.9-67.2)	62.6 (53.3-71.0)
Women	77%	100%	n/a
Smoking	16%	15%	20%
Time from diagnosis, years	7.2 (3.0-17.1)	8.1 (3.1-19.1)	5.1 (2.1-14.1)
RF+	69%	67%	77%
Anti-CCP+	63%	61%	67%
Erosions	55%	55%	54%
TJR[2]	16%	16%	15%
TJC 28	1 (0-2)	1 (0-2)	0 (0-1.5)
SJC 28	0 (0-2)	0 (0-2)	0 (0-1)
CRP	3.0 (1.0-7.0)	3.0 (1.0-7.0)	3.0 (1.0-8.0)
ESR	9.0 (5.0-19.0)	9.0 (5.0-20.0)	7.0 (3.0-16.0)
HAQ-DI[4]	0.63 (0.13-1.1)	0.63 (0.25-1.25)	0.25 (0-1.0)
Inv. global	10.0 (5.0-23.5)	10.0 (5.0-25.0)	10.0 (5.0-20.0)
Patient global	27.0 (10.0-50.0)	29.0 (10.0-50.0)	23.0 (8.0-45.0)
Pain	30.0 (10.0-55.0)	30.0 (10.0-55.0)	20.0 (8.0-45.0)
DAS 28[5]	2.5 (1.7-3.5)	2.6 (1.9-3.6)	2.2 (1.4-3.1)
DAS28 remission	52%	63%	48%

Table 6. (continued)

	Biologic mono-therapy	DMARD+ biologic	DMARD	Glucocorticoids only	No anti-rheumatic medication
N	34 (4%)	150 (17%)	356 (74%)	26 (3%)	24 (3%)
Age	60.5 (46.4-73.3)	55.3 (48.7-64.9)	60.2 (50.4-68.8)	67.9 (57.1-72.1)	57.9 (48.5-67.9)
Women	82%	79%	77%	73%	67%
Smoking	9%	16%	16%	23%	21%
Time from diagnosis, years	18.8 (9.1-29.2)	12.1 (8.0-20.5)	5.2 (2.1-14.1)	23.1 (6.8-38.1)	9.6 (2.9-14.9)
RF+	68%	72%	69%	72%	62%
Anti-CCP+	59%	66%	63%	60%	48%
Erosions	78%	81%	48%	63%	27%
TJR[2]	44%	27%	12%	27%	4%
TJC 28	0.5 (0-2)	1 (0-3)	1 (0-2)	0 (0-3)	0 (0-1)
SJC 28	1 (0-2)	1 (0-2)	0 (0-2)	1 (0-3.5)	0 (0-0.75)
CRP	4.5 (2.7-16.3)	3.0 (1.0-6.5)	3.0 (1.0-7.0)	3.9 (1.1-9.5)	2.0 (1.0-6.8)
ESR	13.0 (7.0-27.3)	11.0 (5.0-22.5)	8.0 (5.0-18.0)	14.5 (5.0-24.5)	7.0 (5.0-15.8)
HAQ-DI[4]	1.0 (0.63-1.7)	0.75 (0.25-1.3)	0.50 (0-1.1)	1.1 (0-59-1.7)	0.25 (0-1.3)
Inv. global	16.5 (8.8-30.0)	14.0 (5.0-25.3)	10.0 (5.0-21.0)	20.0 (5.0-40.0)	2.0 (0-20.0)
Patient global	46.0 (20.5-70.0)	30.0 (11.0-57.8)	25.0 (10.0-47.0)	45.5 (30.0-67.0)	7.5 (0-29.8)
Pain	45.0 (20.0-72.5)	30.0 (12.8-60.0)	26.0 (10.0-50.5)	47.0 (19.0-75.5)	10.0 (1.00-40.0)
DAS 28[5]	3.0 (2.5-3.5)	2.7 (1.9-3.7)	2.5 (1.7-3.4)	2.9 (2.0-4.5)	2.1 (1.1-2.8)
DAS28 remission	28%	44%	54%	42%	68%

[1]Presented as medians with interquartile ranges [2]Total Joint Replacement; [3]mg/l, [4]Without aids and devices, [5]four variables, ESR;

5.2.2 Anti-rheumatic treatment

DMARDs, glucocorticoids and biologic drugs were being used by 91%, 58% and 21 % of patients, respectively while 3.1% were only on glucocorticoids and 2.7% lacked any medication. MTX was the most prevalent DMARD (65%) followed by HCQ (49%) and SSZ (33%). A triple therapy of aforementioned DMARDs was used by 15%, other MTX-based combination by 30%, MTX alone by 20% and other DMARDs alone or in combination by 26% of patients. Mean weekly dose of methotrexate was 17.7mg (median 20.0, IQR 15.0-20.0). Mean number of DMARDs per patient was 1.64 (median 2, IQR 1-2). Complete list of DMARDs and biologics used by the study population are shown in Table 7. Oral glucocorticoids were used by 512 (58%) with a mean daily prednisolone-equivalent dose of 5.6mg (SD 2.8).

Table 7. Drug utilization (adapted from Aaltonen et al. 2014 [219])

Medication	Used by (% of total patients))	DMARDs	Used by (% of patients)
Any anti-rheumatic medication[1]	866 (97%)	Methotrexate	579 (65%)
Synthetic DMARDs	806 (91%)	Hydroxychloroquine	439 (49%)
Biologic drugs	184 (21%)	Sulfasalazine	293 (33%)
Glucocorticoids	512 (58%)	Leflunomide	91 (10%)
Biologic monotherapy	34 (4%)	Gold	30 (3%)
MTX+SSZ+HCQ	88 (15%)	Podofyllotoxin	14 (2%)
		Aazatioprin	10 (1%)
		Ciklosporin	4 (0%)
		Myconofenolate	2 (0%)
		Cyklofosfamide	1 (0%)
		Chloroquine	1 (0%)

[1]Synthetic DMARDs, biologic drugs and glucocorticoids

Overall, there were 184 biologics users of which 82% were using at least one DMARD concomitantly. The most prevalent biologic drugs were etanercept (34%), rituximab (19%), adalimumab (16%) and infliximab (11%). Mean time from diagnosis to initiation of the first biologic treatment was 11.4 years (median 8.0, IQR 4.0-16.0). Biologic monotherapy was most common among the users of anakinra, rituximab, adalimumab and golimumab while abatacept was always used in conjunction with DMARDs. In addition to current biologics users, 54 patients had been on biologic drugs in the past. Thus, overall 30.1% of the cohort had ever been exposed to biologic drugs.

Comparison between men and women revealed numerous differences; compared to women, men with RA were generally older (62.6 years vs. 59.0 years, p=0.002), had a shorter time since diagnosis (5.1 years vs. 8.1 years, p<0.001), were older when diagnosed with RA (53.0 years vs. 45.0 years, p<0.001) were more likely to be positive for RF (77% vs. 67%, p=0.01) and possibly for anti-CCP as well (69% vs. 61%, p=0.065) (table 6). The number of tender (p=0.004) and swollen joints (p=0.005) as well as patient self-assessment of rheumatic activity (29.0 vs. 23.0, p=0.016) were higher among women compared to men. Overall, 63% and 48% of men and women were in DAS28 remission, respectively.

Smokers had higher DAS28 score compared to non-smokers (2.8 vs. 2.5, p=0.001) while higher education was associated with lower disease activity (2.3 vs. 2.8, p=0.001). RF- and anti-CCP status were however similar for smokers and non-smokers alike. Several differences were observed in patient and disease characteristics of users of different medication regimens (Table 7).

5.3 Cohort study on the incidence of serious infections and malignancies (III)

5.3.1 Patients

Of the 3762 patients included in the study, 2217 and 1545 were identified from ROB-FIN and Central Finland Central Hospital, respectively. Of the 4932 medication periods included in the study, 1400 were DMARD therapies and 642, 1245, 1207 and 438 infliximab, etanercept, adalimumab and rituximab therapies, respectively. Disease characteristics and the number of prior biologic treatments differed significantly from each other at baseline (Table 8). Follow-up took place between 1999 and 2011. Altogether, the study medications accumulated 10,994 patient years, lag-time included. The median follow-up times in years in DMARD, pooled TNF-inhibitor, infliximab, etanercept, adalimumab and rituximab groups were 2.3 (IQR 1.2-2.9), 1.5 (IQR 0.57-3.4), 1.6 (IQR 0.81-3.4), 1.5 (IQR 0.50-3.5), 1.3 (IQR 0.50-3.4) and 1.1 (IQR 0.50-2.4) while corresponding sums of patient-years were 3119, 7163, 1700, 2842, 2620 and 712, respectively. The total amount of missing data was 12.4%, ranging from 0 to 26.9% across the variables in the dataset. Complete data were available from 58.2% of the included patients. Results of the sensitivity analysis based on the complete cases were not statistically different from the main results and data were assumed to be missing at random.

5.3.2 Serious infections

Altogether, there were 341 hospitalizations due to infections during the follow-up period, of which 61 were subsequent hospitalizations due to the same infection diagnosis (Table 9). The overall incidence rate of hospitalizations due to all and unique infections were 31 (CI 95 % 28-34) and 25 (CI 95 % 23-29) per 1,000 patient years, respectively. The most frequent infections requiring hospitalization were erysipelas (n=59), infectious gastroenteritis and colitis (n=38), bronchitis (n=31), tuberculosis (n=27) and sepsis (n=22). There were six hospitalizations due to tuberculosis in the sDMARD group while no rituximab treated patient was hospitalized for tuberculosis.

The counts and crude rates of hospitalizations due to an infection were 106 (IR 34, 95% CI 28-41), 198 (IR 28, 95% CI (24-32) 53 (IR 31, 95% CI 23-41), 68 (IR 24, 95% CI 19-30), 77 (IR 29, 95% CI 23-37) and 37 (IR 52, 95% CI 37-72) among the users of sDMARDs, pooled TNF-inbitor, infliximab, etanercept, adalimumab and rituximab, respectively. The mean length of hospital stay was 7.4 days (SD 5.9) with no statistically significant differences between the treatment regimens. In comparison to sDMARDs, results adjusted for age and gender showed a statistically significant increase in the incidence for hospital admission due to infection for infliximab, adalimumab and rituximab. The full model did not however, recognize any single biologic more harmful than sDMARDs. No statistically significant differences were observed in direct comparison between TNF-inhibitors and rituximab after adjusting for all observed confounders. Sensitivity analysis excluding subsequent hospitalizations due to same infections did not statistically significantly alter the results (results not shown). From the potential confounders, age, history of previous hospitalizations due to infections, HAQ score and use of cortisone predicted increased risk for hospitalization due to an infection. Meanwhile, the use of methotrexate and sulfasalazine was associated with a reduced infection risk. In the comparison between TNF-inhibitors and rituximab, prior biologic drug use was not associated with increased or decreased incidence of serious infections.

Table 8. Patient characteristics at the beginning of the follow-up (median and interquartile range). (adapted from Aaltonen et al. 2014 [220])

	sDMARD (n=1,400)	TNF-inhibitors (n=3094)	Infliximab (n=642)	Etanercept (n=1245)	Adalimumab (n=1207)	Rituximab (n=438)	P-value*
Age	62 (53-72)	54 (45-61)	52 (44-59)	54 (45-61)	55 (47 -62)	59 (52-67)	<0.001
Gender, female (%)	69%	75%	72%	76%	76%	77%	<0.001
Time from diagnosis	9.4 (5.0-13)	11 (6.0-19)	11 (5.8-17)	11 (5.8-19)	12 (6.4-20)	15 (8.7-23)	<0.001
Year of the beginning of the follow-up	2009 (2008-2010)	2006 (2004-2008)	2003 (2002-2007)	2006 (2004-2009)	2006 (2005-2008)	2009 (2008-2010)	<0.001
RF-positive (%)	65%	78%	78%	77%	78%	88%	<0.001
DAS28	3.2 (2.2-4.3)	4.4 (3.2-5.5)	4.8 (3.6-5.8)	4.2 (3.0-5.3)	4.3 (3.2-5.4)	4.5 (3.3-5.4)	<0.001
HAQ-DI	0.8 (0.28-1.4)	1.0 (0.50-1.5)	1.1 (0.62-1.7)	1.0 (0.50-1.5)	1.0 (0.48-1.5)	1.1 (0.6-1.7)	<0.001
Prior malignancy (%)	5.5%	3.2%	3.0%	3.3%	3.3%	10%	<0.001
Hospitalization due to an infection during past 24 months (%)	3.6%	4.0%	4.2%	3.9%	3.9%	7.8%	<0.001
Baseline use of methotrexate (%)	75%	54%	54%	54%	56%	41%	<0.001
Baseline use of sulfasalazine (%)	31%	22%	22%	22%	22%	17%	<0.001
Baseline use of hydroxychloroquine (%)	41%	28%	28%	28%	28%	25%	<0.001
Baseline use of oral corticosteroids (%)	53%	75%	78%	75%	73%	78%	<0.001
Prior Biologic	0%	31%	12%	37%	36%	63%	>0.001

RF=Rheumatoid Factor; HAQ=Health Assessment Questionnaire – Disability Index; DAS28=Disease Activity Score based on 28 joint count; VAS=Visual analogue scale; CRP=C-Reactive Protein
*Pooled TNF-inhibitor-column excluded from baseline statistical comparison

5.3.3 Malignacies

The number of malignancies during the follow-up was 92, of which 83 were solid cancers and 9 hematologic or lymphatic malignancies. The incidence rate of all malignancies was 8.4 (95% CI 6.7-10) while the rates of solid cancers and hematologic/lymphatic malignancies were 7.6 (95% CI 6.0-9.4) and 0.80 (95% CI 0.37-1.6), respectively (Table 9). The crude rates of malignancies were highest among the users of sDMARDs (IR 12, 95% CI 8.6-17) and rituximab (IR 9.5, 95% CI 3.8-20) and lowest among infliximab-treated patients (IR 5.8, 95% CI 2.8-11). Analyses adjusted did not reveal any statistically significant differences in the incidence rates of malignancies between the users of sDMARDs and biologics or between different biologic agents.

Table 9. Rates of serious infections and malignancies (adapted from Aaltonen et al. 2014 [220])

	sDMARD	TNF-inhibitors	Infliximab	Etanercept	Adalimumab	Rituximab
Patient years	3119	7162	1700	2842	2620	712
Serious infections						
No of hospitalizations	106	198	53	68	77	37
Length of hospitalization in days (mean,SD)	6.3 (3.7)	7.8 (6.7)	9.5 (7.9)	7.3 (5.5)	7.3 (6.7)	7.9 (6.2)
IR / 1000 patient years	34 (28-41)	28 (24-32)	31 (23-41)	24 (19-30)	29 (23-37)	52 (37-72)
IRR (95% CI)	Ref.	0.80 (0.58-1.1)	0.89 (0.58-1.4)	0.70 (0.47-1.0)	0.85 (0.58-1.3)	1.5 (0.90-2.5)
Adj. IRR * (95% CI)	Ref.	1.4 (1.0-1.9)	1.6 (1.1-2.5)	1.2 (0.82-1.8)	1.4 (0.96-2.1)	2.1 (1.3-3.4)
Adj. IRR** (95% CI)	Ref.	0.9 (0.6-1.4)	1.2 (0.63-2.3)	0.84 (0.53-1.3)	0.98 (0.60-1.6)	1.1 (0.59-1.9)
Malignancies						
No of malignancies	39	47	10	21	16	6
IR / 1000 patient years	13 (8.9-17)	6.6 (4.8-8.7)	5.9 (2.8-11)	7.4 (4.6-11)	6.1 (3.5-9.9)	8.4 (3.1-18)
IRR	Ref.	0.52 (0.34-0.80)	0.46 (0.23-0.93)	0.59 (0.35-1.0)	0.49 (0.27-0.88)	0.68 (0.29-1.6)
Adj. IRR*(95% CI)	Ref.	0.98 (0.61-1.57)	0.91 (0.44-1.9)	1.1 (0.63-2.0)	0.87 (0.47-1.6)	1.0 (0.42-2.4)
Adj. IRR**(95% CI)	Ref.	1.2 (0.63-2.2)	1.2 (0.44-3.1)	1.3 (0.65-2.6)	1.1 (0.51-2.2)	1.2 (0.49-3.2)

* Age and gender; **Full model

5.4 Cohort study on the incidence of joint replacements (IV)

5.4.1 Patients

Overall, 2102 biologics users and 2710 DMARD users were identified from ROB-FIN and the Central Finland Central Hospital. There were numerous differences in patient characteristics between DMARD and biologics users before matching (Table 10). Biologics users were more often females, were younger and had had more joint replacements prior to follow-up. Patients in the biologics group also had a longer time from the diagnosis of RA to the initiation of follow-up and higher HAQ scores than their DMARD using comparators. After PSM, the number of patients was reduced to 1587 in both groups while most differences in background data disappeared. Despite matching, small but statistically significant differences were observed in HAQ scores and time from RA diagnosis. One or more disease activity measurements were missing from 16.0% and 27.5% of biologics and DMARD users, respectively.

Table 10. Patient characteristics in matched and unmatched populations (adapted from Aaltonen et al. 2013 [221])

	Unmatched population			**Matched population**		
	Biologics	sDMARDs	p-value	Biologics	sDMARDs	p-value
Number of patients	2102	2710		1587	1587	
Patient years	8326	19421		6146	11762	
Age[1]	53.3 [52.1] (14.23 - 84.22)	61.5 [59.9] (14.27 - 93.94)	*<0.001*[3]	55.1 [53.9] (16.77 -84.22)	54.6 [54.0] (14.27 -87.42)	*0.406*[3]
Women	74.1%	70.0%	*0.001*[4]	71.8%	71.1%	*0.666*[4]
Time from diagnosis[1, 2]	9.7 [11.9] (-5.13 - 54.54)	5.5 [8.0] (-5.29 - 63.55)	*<0.001*[3]	9.7 [10.8] (-5.13 - 48.72)	9.7 [11.0] (-5.29-63.55)	*0.019*[3]
HAQ[2 6]	0.84 [0.90] (0 - 3)	0.63 [0.82] (0 - 3)	*<0.001*[3]	0.81 [0.87] (0 - 2.94)	0.71 [0.86] (0 - 3)	*<0.001*[3]
Patient global[2] (VAS 0-100mm)	35.3 [36.8] (0 - 100)	38.0 [37.9] (0 - 100)	*0.074*[3]	36.5 [37.6] (0-100)	37.8 [37.2] (0-100)	*0.684*[3]
Rheumatoid factor-positive	79.1%	67.2%	*<0.001*[4]	76.4%	77.0%	*0.728*[4]
Joint replacement prior to follow-up	19.4%	13.4%	*<0.001*[4]	16.5%	16.0%	*0.700*[4]
N of joint replacements prior to follow-up[2 5]	2 [2.07] (0 - 8)	2 [1.80] (0 - 6)	*0.101*[3]	2 [1.96] (0 - 8)	2 [1.92] (0 - 6)	*0.530*[3]

[1] At the beginning of the follow-up
[2] Median [mean] (range)
[3] Mann-Whitney U-test
[4] Chi-Square test
[5] Of patients who have one or more joints replaced prior to follow-up
[6] (Health assessment questionnaire)

Follow-up period in the control group began 4.5 years earlier and ended one year earlier compared to biologics users. The median duration of follow-up periods in the biologics and DMARD groups were 3.1 (0.04-10.05) and 8.0 (0.02-12.94), respectively. Thus, DMARD group accumulated nearly twice as many patient years as the biologics group did. While biologics users had received their first joint replacement 11.2 (median, range -20.1-52.4) years after the diagnosis, the corresponding time for DMARD users was 14.7 (-6.1-54.3) years.

5.4.2 Primary joint replacement operations

Altogether, 813 primary joint replacements were performed during the follow-up of which 550 among the matched population. The number of patients undergoing at least one primary joint replacement operation was in 410 (12.9%). The overall incidence rate of primary operations per 100 patient years was 2.93 (2.73-3.14). Patients in the biologics group had higher incidence rate of joint replacements than the DMARD group in matched population (Table 11). While the rates of hip operations were similar, operations of the knee and other joints were more common among biologics users. The most common indication for joint replacement surgery was RA in both biologics and DMARD groups (86% and 79% of operations in matched population, respectively). The second most common reason for operation was primary osteoarthritis in both groups.

Table 11. Numbers of joint replacement operations in the matched populations during follow-up (adapted from Aaltonen et al. 2013 [221])

	Joint replacements		**Incidence rate per 100 patient years (95% CI)**[1]	
	Biologics	sDMARDs	Biologics	sDMARDs
Primary operations	240	310	3.90 (3.42-4.43)	2.64 (2.35-2.95)
Hip	58 (24.2%)	105 (33.9%)	0.94 (0.72-1.22)	0.89 (0.73-1.08)
Knee	101 (42.1%)	131 (42.3%)	1.64 (1.34-2.00)	1.11 (0.93-1.32)
Other joints	81 (33.8%)	74 (23.9%)	1.32 (1.05-1.64)	0.63 (0.49-0.79)
Reason for primary operation				
Rheumatoid arthritis	206 (85.8%)	246 (79.4%)	3.35 (2.91-3.84)	2.09 (1.84-2.37)
Other arthritis	0	1 (0.3%)	0.00 (0.00-0.06)	0.01 (0.00-0.05)
Primary osteoarthritis	28 (11.7%)	47 (15.2%)	0.46 (0.30-0.66)	0.40 (0.29-0.53)
Secondary osteoarthritis	4 (1.7%)	0	0.07 (0.02-0.17)	0.00 (0.00-0.03)
Other reason	2 (0.8%)	16 (5.2%)	0.03 (0.00-0.12)	0.14 (0.08-0.22)
Revision operations	40	98	0.65 (0.46-0.89)	0.83 (0.68-1.02)
Hip	17 (42.5%)	59 (60.2%)	0.28 (0.16-0.44)	0.50 (0.38-0.65)
Knee	7 (17.5%)	25 (25.5%)	0.11 (0.05-0.23)	0.21 (0.14-0.31)
Other joints	16 (40.0%)	14 (14.3%)	0.26 (0.15-0.42)	0.12 (0.06-0.20)
Reason for the revision				
Loosening	8 (20.0%)	17 (17.3%)	0.13 (0.06-0.26)	0.14 (0.08-0.23)
Infection	6 (15.0%)	12 (12.2%)	0.03 (0.00-0.12)	0.10 (0.05-0.18)
Other reason or missing	26 (65%)	69 (70.4%)	0.42 (0.28-0.62)	0.59 (0.46-0.74)

[1]Poisson distribution

Survival analysis of the proportion of patients undergoing primary joint replacement operation during the follow-up time reveals a statistically significant difference considering small joint operations (Figure 6). However, survival without any hip or knee operations during the follow-up was similar.

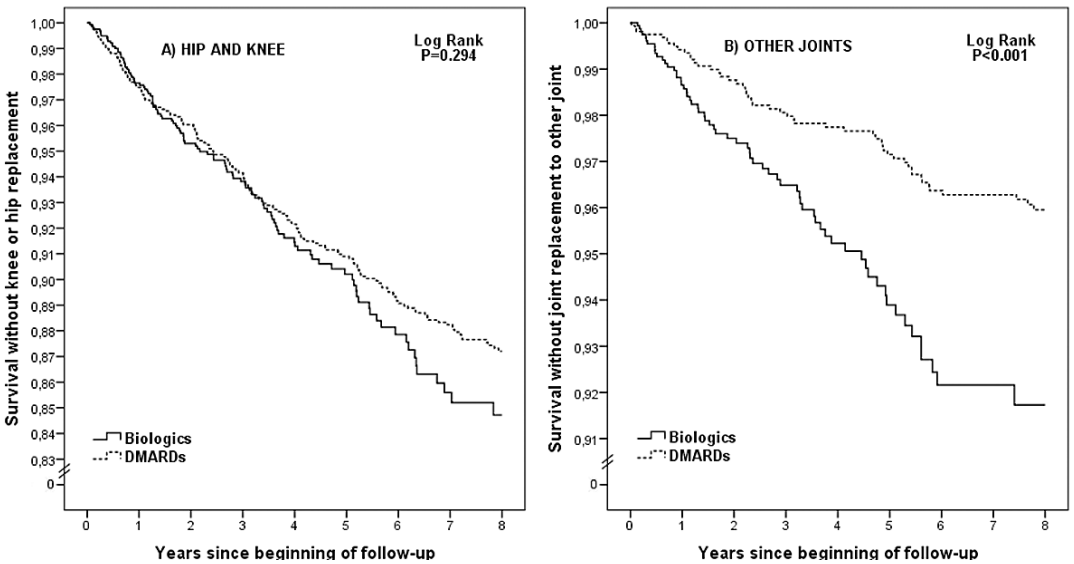

Figure 6. Kaplan–Meier survival plots indicating the percentage of patients without joint replacements to either (A) hip and knee or (B) other joints during the follow-up (Aaltonen et al. 2013 [221]).

5.4.3 Revision operations

Primary operations performed within follow-up in matched and unmatched populations were revised in 67 (8.4%) and 31 (5.7%) cases, respectively. The incidence rate of revisions appeared lower in the biologics (0.65, 0.46-0.88) group than in the DMARD group (0.83, 0.68-1.01) (Table 11). The difference was mostly due to lower rates of hip and knee revisions (although there were no statistically significant differences) and in the rate of other joint revisions the situation was the opposite. There were no statistically significant differences between biologics and DMARD users in reasons for revision.

The survival of the joints replaced prior to follow-up appeared similar in the biologics group compared to DMARD users both in hip and knee (p=0.450) and other joints (p=0.571) (Figure 7). The primary surgery had taken place 5.2 (median, range 0.1-25.0) and 5.3 (0.01-22.1) years before the follow-up in biologics and DMARD groups with no

statistical difference (p=0.924), respectively. The results for prostheses installed during follow-up suggested that while the biologics users might have better survival of hip and knee joint replacements (p=0.236), the situation was reversed regarding other joints (p=0.278) (Figure 8).

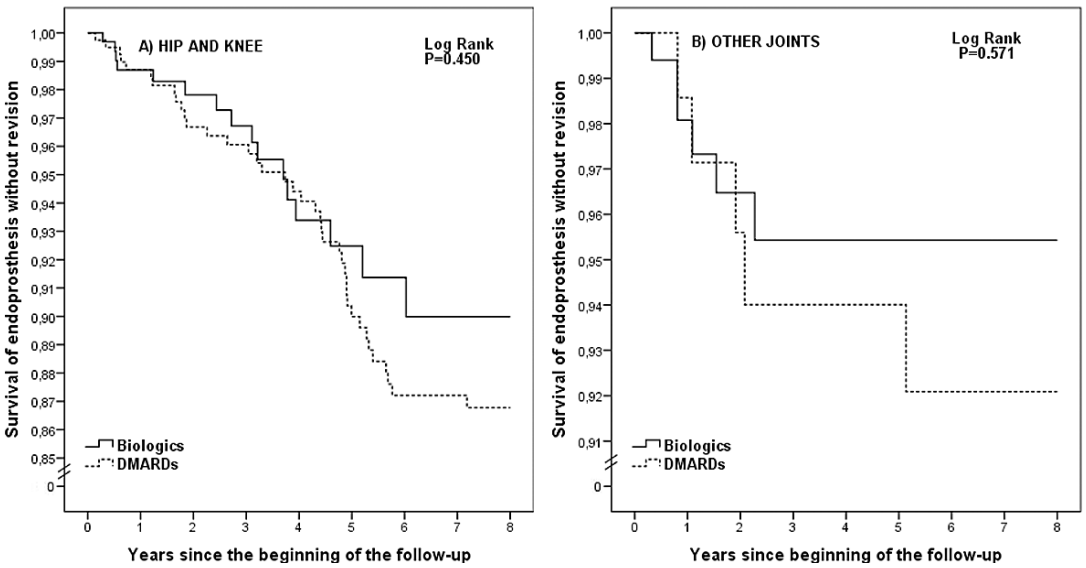

Figure 7. Survival without revisions in joint replacements either to (A) hip and knee or (B) other joints installed prior to follow-up (Aaltonen et al. 2013 [221]).

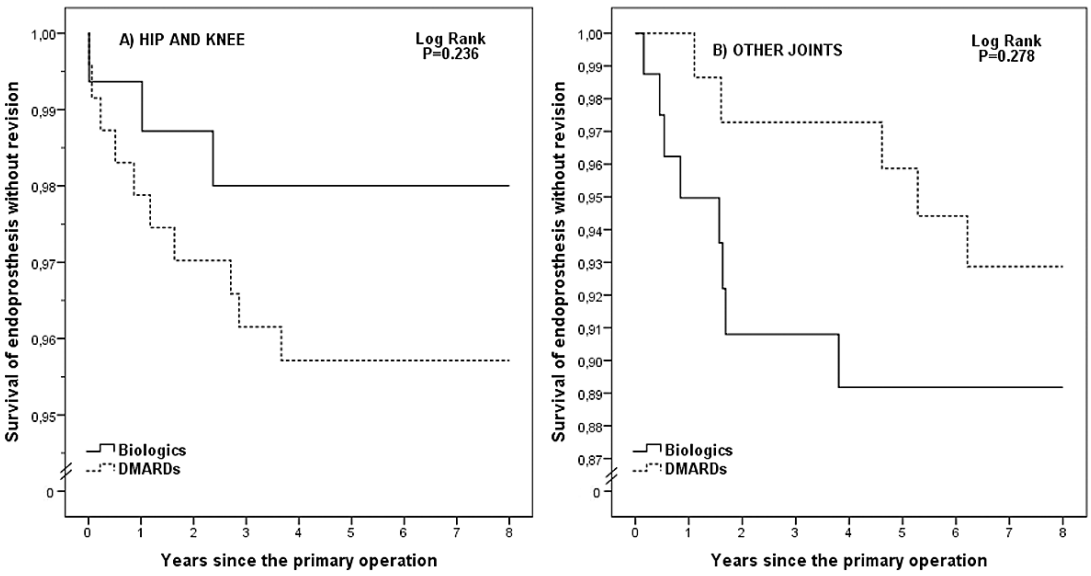

Figure 8. Survival without revisions in joint replacements either to (A) hip and knee or (B) other joints installed during follow-up (Aaltonen et al. 2013 [221]).

5.4.4 Sensitivity analyses

There were no statistically significant differences between the rates of primary operations between the biologics users identified from ROB-FIN or Central Finland Central Hospital. Biologics users with follow-up longer than 9.5 years have lower incidence rate of primary operations (2.27, 95% CI 1.61–3.12) compared to un-stratified results, which was not the case among sDMARD treated patients (2.72, 95% CI 2.32–3.13). Patients with missing data had shorter follow-up times compared to patients with complete data. Biologic users with missing data had a higher incidence rate of operations compared to complete cases, but only accounted for 8.1% of the patient years.

6 DISCUSSION

6.1 General discussion

The studies included in this thesis evaluated the efficacy, safety, outcomes and utilization of biologic DMARDs in the treatment of RA. Firstly, we identified, evaluated and pooled all relevant RCTs on the efficacy and safety of TNF-inhibitors in treatment of RA. Secondly, a cross-sectional overview was performed to describe the disease characteristics and medical treatment of prevalent RA patients in Finnish outpatient specialized healthcare. Thirdly, we executed two cohort studies comparing the incidence of joint replacement surgery, serious infections and malignancies between the users of biologic and synthetic DMARDs. The results of our studies aim at strengthening the existing knowledge of the biological DMARDs as a treatment alternative in RA, especially within the Finnish healthcare environment.

6.2 Data collection and methods

6.2.1 Systematic review (I)

Systematic review is a method of research narrating all empirical evidence on subject with well-defined eligibility criteria and research question [155]. It features thoroughly documented and reproducible methodology aimed to identify, select and evaluate all relevant previously published data. Many systematic reviews contain meta-analyses, which are statistical methods to summarize the results of the independent studies. To date, only two major RCTs comparing biologic drugs to one another have been performed [222]. Undertaking a systematic review and a meta-analysis allowed us to indirectly compare the efficacy and safety of all five TNF-inhibitors available at the time. The literature search was designed for sensitivity rather that specificity and as a consequence, we identified over 5454 references, of which 3841 were manually evaluated by two persons by title and abstract. Subsequently, 76 potentially relevant full-text articles were evaluated for inclusion. Forty publications reporting of 26 RCTs were included with 6780 and 3082 patients in intervention and control groups, respectively. As the study featured studies with different TNF-inhibitors and comparators, several subgroup analyses were undertaken. Some heterogeneity in the results of the included RCTs was present and as a result, random effects model was used in the meta-analyses.

6.2.2 Cross-sectional study (II)

Studies on RA often focus on a particular subgroup defined by a distinct condition or treatment. Cross-sectional study on the other hand, is a study which includes all persons in the population, or a representative sample of all such persons, selected without regard to exposure or disease status [223]. Cross-sectional studies have been performed in Finland, but not on a nation-wide scale [224]. We invited Finnish outpatient specialized healthcare clinics to enroll consecutive patients with the aim of reaching a representative sample of 1000 patients with RA. A purpose-made data collection form was used comprising questions on the patients' disease characteristics, medical treatment and socioeconomic factors. The questionnaire featured several scores and indices such as DAS28, SDAI and CDAI with the aim of promoting their use in routine healthcare. One of the clinics participating in the study used an electronic patient monitoring software to collect the data instead of paper data collection forms. However, the same variables were collected and the same inclusion criteria for patients were employed in clinics utilizing either manual or electronic data collection.

6.2.3 Cohort studies (III and IV)

Several studies have compared the inclusion criteria of major RCTs and the characteristics of RA patients using biologic drugs in routine clinical practice and found that only a small subset of RA patients would have been eligible for those trials, limiting their generalizability [12,225]. Furthermore, the relatively short follow-up times and limited number of included patients may be insufficient to reveal rare, delayed or long-term outcomes. Therefore, observational research based on large cohorts of true users with long exposure times can supplement the information provided by RCTs. Also, RCT studies are very costly and in some cases unethical whereas most observational studies require less resources and study personnel to perform. Many countries, especially Nordic countries, have healthcare registers with mandatory data collection, facilitating good quality retrospective register studies. Following the introduction of TNF-inhibitors to clinical use, rheumatologists in European countries established prospective cohort studies to monitor the safety and effectiveness of the new therapies [226]. The Finnish biologics register, namely the national register for biologic treatment in Finland (ROB-FIN) was founded by the Finnish Society of Rheumatology and includes patient data from 1999 onwards. Inclusion to ROB-FIN required patients' informed consent and was voluntary for the rheumatologist. Coverage has been estimated to be 60% of all RA patients treated with bDMARDs in Finland [227].

Our cohort studies were based on a mixture of prospectively and retrospectively collected data. The patients included in our cohort studies were identified from three sources; ROB-FIN, hospital records of the Central Finland and an annual survey-based time-series performed in the Jyväskylä region. The survey data was used to extend the length of the follow-up in study IV as it was deemed necessary considering the delayed nature and low incidence of the joint replacement operations. Information entry to the national registries for hospitalizations, malignancies and joint replacement operations is mandatory in Finland thus providing an unbiased source for medical outcomes. The data on malignancies dates back to 1953 and has been shown to be complete in solid tumors and near-complete in lymphatic malignancies [228]. Patients with history of malignancies were included in the study, but only four recurrent malignancies were observed. Also, information on prior malignancies, serious infections during the past 24 months and prior joint replacement operations were used as confounders in the multivariate analyses, which were undertaken to account for the differences between sDMARD and biologic drug users either by providing adjusted IRRs or for the purposes of matching. In study IV, biologic drug users were pooled to increase statistical power due to the low incidence of joint replacement operations while in study III the users of infliximab, etanercept, adalimumab and rituximab were analyzed separately.

6.3 Efficacy of the biologic DMARDs in the treatment of RA

Our systematic review (I) confirmed that as a group, TNF-inhibitors are more efficacious than comparator treatments in general. However, stratification of the trials by the choice of comparator and the use of concomitant MTX has significant impact on the effect size. Without concomitant MTX treatment, TNF-inhibitors are more efficacious than placebo but equal to MTX. The combination of TNF-inhibitor and MTX is however, superior to monotherapy with either TNF-inhibitor or MTX. Prior exposure to MTX increased the observed difference between TNF-inhibitor and MTX groups, suggesting that treatment with bDMARDs is more efficacious among patients with insufficient treatment response to MTX as compared to MTX-naïve patients. Differences in the RRs for reaching the treatment response between individual TNF-inhibitors are subtle, but according to our results infliximab and golimumab are not associated with statistically significantly improved treatment response over the comparator. The apparent lack of response might however, be explained by insufficient statistical power and heterogeneity in the inclusion and exclusion criteria as compared to studies of other TNF-inhibitors. Increased doses of TNF-inhibitors were not associated with improved treatment response in comparison to normal doses.

A previous systematic review and meta-analysis pooled efficacy results from different time points and found slightly different estimates for the efficacy of TNF-inhibitors, which is likely due to differences in the methodology of the systematic reviews and meta-analyses [229]. Also several large clinical trials have been published since the aforementioned review along with the introduction of two novel TNF-inhibitors, certolizumab pegol and golimumab. More recently, Nam et al. performed a systematic review including all biologic DMARDs, focusing solely on the efficacy measured by reaching ACR 70 response [230]. Besides confirming our results on the effect of prior MTX treatment on the efficacy of TNF-inhibitors, they also found that the differences between individual bDMARDs are subtle. In head-to-head studies of bDMARDs, the combination of abatacept and MTX was similar in efficacy as the combination of adalimumab and MTX, yet monotherapy of tocilizumab was more efficacious as compared to monotherapy of adalimumab [20,231]. Several studies were found by Nam et al., which explored the possibility of discontinuing the treatment or alternatively, reducing the dosage of TNF-inhibitor after the initial treatment response had been achieved [230]. Although the maintenance of low disease activity is better with bDMARD continuation at full dose, high drug expenditures warrant further research to disclose if early treat-to-target approach and subsequent drug discontinuation or dose reduction would be cost-effective. Regarding the similar efficacy of increased dose of TNF-inhibitors compared to normal doses, another previous systematic review reached the same conclusion as we did [22]. Lately, several studies have compared treatment with the combination of bDMARDs and sDMARDs to intensified treatment with sDMARDs, in most cases the triple therapy consisting of MTX, SSZ and HCQ [230]. Most such studies have found both equal in clinical efficacy with radiographic progression possibly better delayed by the bDMARD [15,16,109]. In accordance with our results, Nam et al. found that the combination of bDMARD and sDMARD is more efficacious in comparison to monotherapy of bDMARD, except possibly among the patients with prior incomplete treatment response to MTX [230].

A biosimilar infliximab authorized by EMA for treatment of RA, CT-P13 was directly compared against innovator infliximab [232]. A RCT with more than 600 patients was unable to show any statistically significant differences between the efficacy of the innovator and the biosimilar infliximab, measured as ACR20 response at 30 weeks. Similar findings were seen among patients with ankylosing spondylitis, as well [233]. This implies that the results of our systematic review are generalizable to the currently available and probably also to upcoming biosimilar DMARDs. Further research is however, warranted.

Owing to the stringent inclusion criteria for RCTs, the results of the randomized clinical trials may no be fully generalizable to routine care. In European countries, the proportion of patients starting their first biologic eligible for RCTs has ranged from 21 to 79 per cent [12,234,235]. Observational trials have shown that majority of the patients treated with bDMARDs in routine care benefit from the treatment with the RCT eligible patients having superior effectiveness results in comparison to those not eligible. In accordance to our systematic review based on RCTs, no TNF-inhibitor has been deemed superior to other in studies based on observational data [111–114]. Opinions and results on whether the cost-effectiveness results based on modelling studies utilizing data from RCTs are generalizable to routine case are not coherent [235–237]. Generalization of results derived from RCTs to routine clinical practice might be further hindered by high percentages of patients switching between treatment arms, often from placebo to active treatment owing to the lack of treatment response. As the results are often reported using intention-to-treat protocol, the true length of exposure among placebo-treated patients might be less than among patients treated with active treatment. On the other hand, a high incidence of adverse events in the active treatment group might lead to opposite results.

The current treatment guidelines by EULAR suggest commencing the treatment of a recent RA with MTX or a combination of sDMARDs in addition to low-dose glucocorticoids [8]. Biologic drugs including TNF-inhibitors, toclizumab, abatacept and rituximab in certain conditions are recommended for patients with incomplete response to sDMARDs. In the light of our findings of biologic drugs being more efficacious among patients with incomplete response to MTX as compared to MTX naive patients, the EULAR recommendation on starting treatment with sDMARDs seems justified. We found that there are only few differences between TNF-inhibitors in efficacy and consequently, the guidelines do not raise any single substance over another. Moreover, they consider tocilizumab, abatacept and even rituximab as plausible alternatives as the patients' first biologic treatment, the conclusions of which are mainly based on the recent systematic review by Nam et al. [230].

6.4 Disease characteristics and the use of biologic and synthetic DMARDs in treatment of RA in Finland

6.4.1 Disease characteristics

A cross-sectional (II) study aimed to provide a nationwide overview on patients with RA in Finland; the RAMI project included consecutive patients from participating clinics, covering information on patient background, disease activity and medical treatment. The included patients had a median age of 59.8 years while 23% were men, which are similar as described in previous studies [224,238,239]. The included cohort had a median DAS28 value of 2.55 with 52% and 70% of patients reaching remission and low disease activity, respectively. An international cross-sectional study published in 2007 included also three clinics from Finland whose patients had a median DAS28 of 3.1 [224]. Therefore, it could be postulated that the average disease activity of prevalent RA cases has decreased during the past six years. In contrast however, the median disease activity of sDMARD users included in the cohort studies was higher than either in ours or in the previous cross-sectional study [224].

The median DAS28 at the baseline of TNF-inhibitor treatment among the patients included in the cohort study on serious infections and malignancies (III) was 4.4 (IQR 3.2-5.5), which as expected, was higher as compared to that of prevalent biologic drug users within the cross-sectional study (II). While the median HAQ score at the baseline of TNF-inhibitor treatment in the cohort study (III) was 1.0, the corresponding score varied between 1.25 and 1.88 among the RCTs included in the systematic review (I). This implies that the patients included in the RCTs have a more severe RA as compared those treated in routine healthcare, which has been documented in other countries as well [12].

In the cross-sectional RAMI study (II), remission rates based on the ACR/EULAR criteria differed significantly from those based on DAS28 score, confirming that the former are more stringent than the latter [240]. We found a significant difference between patient and investigator global assessments, which might be due to physicians and patients focusing on different aspects of the disease in their respective evaluations [241]. Tobacco smoking is an environmental factor contributing to the severity of rheumatoid arthritis and we found in our study that tobacco-smokers have a higher disease activity compared to non-smokers [242,243]. However, a prior international study found an opposite trend, which might suggest that the effect of smoking on disease activity is confounded by other factors such as socioeconomic status and drug adherence [244]. In 2011, 22% and 15% of Finnish inhabitants men and women aged between 15 and 64 were current smokers, respectively [245]. As the corresponding percentages in study II were found to be 20%

and 15%, respectively it is plausible to assume that the smoking habits of RA patients do not significantly differ from those of the general population.

According to the results of study II, men are older than women when diagnosed with RA, which is in accordance with the previous evidence on later onset of RA among men [246,247]. RF was evident in 77% and 67% of men and women, respectively. Differences between sexes in both in time from diagnosis and RF status might be different underlying pathological processes of RA [38,46]. Women also have a more active disease as compared to men, yet with similar erosive progression. Controversially, biologic treatments had been initiated earlier for men in comparison to women.

6.4.2 Medical treatment

Overall penetration of disease-modifying anti-rheumatic therapies observed in the cross-sectional study (II) was very high, considering that recent Swedish study identified only 76% of RA patients as current or past users of anti-rheumatic medication [239]. A previous cross-sectional study does nevertheless, support our results [224]. The inconclusive results may be explained to some extent by the different study designs and different methods for identifying the included RA patients. MTX was the most commonly used sDMARD followed by HCQ and SSZ in both our studies II and III as well as in prior studies [224]. The RACo-combination was used by 15% of the patients in study II while 58% of the patients were currently using oral glucocorticoids. Any biologic treatments were used by 21% of the patients, which is twice as high as in the year 2006 [224]. The use of bDMARDs varies greatly between countries. However, as shown by Sokka et al., prevalent disease activity does not necessarily correlate with high penetration of biologic treatments [224,248]. The apparent lack of correlation may however, be confounded by unmeasured differences in the severity of the disease. Instead, prevalent disease activity is clearly associated with the gross domestic product of the country, but whether this effect is mediated via low access to treatment or other factors such as low socioeconomic status is unclear [249]. According to the results of study II, the first biologic treatment was initiated 8 years after the diagnosis while the time from diagnosis to the baseline of the first TNF-blocker in study III was 11 years. Studies from other countries are more in line with the former, but it should be taken into account that the data collection for study II took place between 2011 and 2012 while the data for the cohort studies ranges from 1999 to 2011 [112,113].

Study II showed that the patients on biologic monotherapy had a higher DAS28 and HAQ scores compared to patients on sDMARDs or combination of biologics and sDMARDs. Also, the patients on biologic monotherapy had the longest time since diagnosis, which

could mean that all possible sDMARDs have already been tried and subsequently discontinued and hence, biologic monotherapy would have been used as a last resort. Biologic monotherapy was most common among the users of anakinra, rituximab and adalimumab. However, the low number of anakinra-treated patients limits the generalizability of the finding. Although the authorization details of infliximab call for concomitant MTX treatment, 15 per cent of the infliximab users had no ongoing concomitant sDMARD therapy. In study III, only 54% of infliximab users were on MTX at baseline. Lack of concomitant sDMARD therapy among infliximab-treated patients may be suboptimal since concomitant use of MTX has been shown to reduce the risk of treatment discontinuation, probable owing to the prevention of anti-drug antibody formation [74,113]. Controversially, the patients on no ongoing active antirheumatic medication had the lowest disease activity of all medication strategies. This finding is not clearly explained by the data, but one could speculate that these patients had been treated to remission or low disease activity with prior treat-to-target medication strategy or alternatively, some of the patients included in this group could be pregnant.

Based on our results it is not possible to evaluate if Finnish and European treatment guidelines have been followed since we do not have data on the prior treatment and medical history [7,8]. Of the rituximab users included in the study III, 37% had not been treated previously with prior bDMARDs. Although the most recent EULAR guidelines warrant the use of rituximab as the first choice for biologic treatment under certain conditions, the data for the study has been collected prior to the publication of the latest iteration of the guidelines. Rituximab users had a greater percentage of prior serious infections and malignancies compared to TNF-treated patients and rituximab could have been considered a safer alternative in presence of aforementioned medical history.

6.5 Safety and outcomes of biologic DMARDs in treatment of RA

6.5.1 Discontinuation due to adverse events

The results of our systematic review (I) revealed TNF-inhibitors as a group equal to comparator treatment in terms of discontinuations due to adverse events, which was already noted by a previous study [22]. A subgroup analysis however, revealed that TNF-inhibitors in combination with MTX were associated with increased risk for discontinuation owing to adverse events in comparison to MTX alone (RR 1.37 95% CI 1.01-1.87). On the other hand, a comparison between TNF-inhibitor monotherapy and placebo failed to show statistical significance despite a strong trend (RR 1.90, 95% CI 0.94-3.84), possibly due to the heterogeneity between the included studies. Safety of TNF-inhibitor and MTX were similar with a weak trend favoring the former. There were some

differences between individual agents. Etanercept was associated with reduced likelihood to discontinue treatment due to adverse events while infliximab, adalimumab and certolizumab pegol were associated with more discontinuations than the comparator, which is in accordance to results of previous systematic reviews [21,22]. Elevated dosing of TNF-inhibitors was comparable to normal dosing in terms of discontinuations due to adverse events (RR 0.98 95% CI 0.72-1.35). However, the proportion of patients experiencing any adverse event was statistically significantly lower among the patients treated with higher than normal doses. In a Danish observational study, 9% and 17% of patients discontinued TNF-inhibitor treatment within 6 and 48 months after the treatment onset owing to adverse events, respectively with no statistically significant differences observed between infliximab, etanercept and adalimumab in adjusted survival analysis [112].

6.5.2 Injection and infusion reactions

As a group, TNF-inhibitors increased the risk for injection or infusion reactions (RR 2.46, 95% CI 1.63-3.70). The risk of experiencing an infusion reaction following the administration of infliximab was lower among the elevated dosing group, which might be due to greater immunosuppressive effect and subsequently reduced immunogenicity. However, there was considerable heterogeneity in the relative risk for injection or infusion reactions, hindering any conclusions based on subgroup analyses.

6.5.3 Serious infections

In our cohort study (III), the crude incidence rate of serious infections per 1000 patient years among the TNF-inhibitor users was 28 (95% CI 24-32) while the corresponding incidence rates in previous studies have ranged from 26 to 55 [24,128,131]. The comparison of results based on observational studies from different may however, be thwarted by the differences in the definition of serious infections, selection of study participants and study methodology. Twenty-Seven cases of tuberculosis were observed of which most among TNF-inhibitor-treated patients and none among rituximab users. As TNF-inhibitors are known to predispose to reactivation of latent tuberculosis, tuberculosis is nowadays screened for and treated if necessary, before commencing the biologic anti-rheumatic treatment [250].

Etanercept and infliximab users had the lowest (IRR 0.84 95% CI 0.53-1.3) and the highest (IRR 1.2 95% CI 0.63-2.3) incidence rate ratios for serious infections in comparison with sDMARDs, respectively although these differences were not statistically significant. Rituximab was comparable in terms of the incidence of serious infections to both TNF-inhibitors and sDMARDs. Some of the patients included in the study III experienced

multiple episodes of hospitalizations due to infections. British guidelines suggest that treatment with TNF-inhibitors should be discontinued in the presence of serious infections, but may be commenced again once the infection has resolved [251]. Subsequent hospitalizations due to same infection diagnosis could be correlated and thus in violation of Poisson distribution and therefore, we performed a sensitivity analysis by excluding multiple hospitalizations due to same infection. This did not however, change the results in a significant manner (data not shown). Length of the hospital stay was not statistically significantly different between the users of sDMARDs, TNF-inhibitors or rituximab, which suggest that the severity of infections was similar among the treatment groups and that there was no subsequent tendency to hospitalize the users of either group more easily, given that the physician was aware of the patients' exposure to immunosuppressive treatments. Post-operative infections were excluded from study III due to a dissimilar rate of arthoplastic surgery among DMARD and biologics users in Finland, which could have biased the results [221]. However, the study IV revealed no statistically differences in the incidence of post-operative infections following a joint replacement operation.

The systematic review (I) showed a risk for serious infections between TNF-inhibitor and comparator groups (RR 1.40 95% 0.93-2.10) to be statistically insignificant although a slight trend towards increased risk was evident. Our cohort study (III), however, found no such trend after adjusting for confounding (IRR 0.9 95% CI 0.6-1.4) while previous observational cohort studies identified by a systematic review by Ramiro et al. have acquired adjusted estimates ranging from 1.1 to 2.4 [24,128,133]. Our adjusted estimates for IRR are nevertheless, within the 95% confidence intervals of previous studies. Also, the choice of variables included in the model as confounders plays a major role as evidenced by study III. Adjustment for age and sex only produced statistically significant IRRs for infliximab and rituximab in comparison to sDMARD users. The same pattern was previously observed by Dixon et al, highlighting the importance of clinical data on disease characteristics of the patients [252]. Although eight previous observational studies on the incidence of serious infections during exposure to TNF-inhibitors were identified by a systematic review, a meta-analysis was not warranted given the heterogeneity of the included studies [24].

The increased risk for serious infections among TNF-inhibitor users in comparison to sDMARD-treated patients has been observed to be highest during the first six months of treatment onset [123]. This might be partially so because the TNF-treated patients susceptible to infections were excluded from the analysis after their first outcome, enriching the remaining population with more infection-resistant patients. Patients

treated with sDMARDs, on the other hand, have been taking those drugs for a period of time and the infection-susceptible patients may have discontinued their use prior to follow-up [253]. The so called prevalent-user bias may be evidenced by MTX and SSZ being statistically significantly associated with decreased incidence of serious infections in our study III. Concomitant use of oral glucocorticoids, history of serious infections, age and HAQ score were statistically significant confounders for increased incidence of infections. We did not include the daily dose glucocorticoids in our statistical model, but a previous study found a dose-dependence between the use of glucocorticoids and the incidence of serious infections [132].

6.5.4 Malignancies

The crude rates of malignancies were highest among the users of sDMARDs and rituximab and lowest among infliximab-treated patients, but adjusted results proved this finding to be confounded. As a group, TNF-inhibitors were not associated with elevated risk for malignancies (IRR 1.2 95% CI 0.44-3.1). Previous studies have found similar or even lower estimates, confirming that TNF-inhibitors are unlikely to predispose to malignancies in general [24,139,142–144]. The risk of melanoma and non-melanoma skin cancer may be increased in patients on TNF-inhibitors, but we were unable to confirm that in our analyses [24]. Only 9 hematologic or lymphatic malignancies were observed, preventing any multivariate analyses. Prior results have, however, concluded that high disease activity and not the exposure to TNF-inhibitor treatment is associated with increased incidence of lymphatic malignancies [136].

6.5.5 Joint replacements

The cohort study on joint replacement surgery comprised 813 primary and 204 revision operations among 4812 patients, accumulating a total of 27744 patient years. After the matching, 240 (IR 3.90 95% CI 3.42-4.43) and 310 (IR 2.64 CI 95% 2.35-2.95) primary operations remained among the biologic and synthetic DMARD users, respectively. The higher incidence of primary operations among the biologic DMARD users compared to sDMARD users was not expected and conflicts with some of the prior reports [17,34]. More recently in a Spanish observational study however, Leon et al. showed incidences rates of 3.1 and 2.35 total joint replacement operations per 100 patient years among the users and nonusers of biologic treatments, respectively, yielding an adjusted odds ratio of 1.95 (95% CI 1.01-3.86) [254]. The annual number of primary joint replacement operations performed due to RA has declined over the past 15 years in Finland, but this does not explain our results since the follow-up of biologics took place later as compared to sDMARD users [35]. It may be that the matching in cohort study (IV) failed to account

for the underlying differences in disease severity and erosive progression between the biologic and synthetic DMARD users. Furthermore, while biologic drugs have been shown to reduce or delay the erosive progression, they do not reverse the damage already occurred [230]. Previous studies have shown that the patients' first total joint replacement operations takes place in average eight years after the diagnosis while the corresponding median time in our study was 11 and 15 years for the users of biologic and synthetic DMARDs, respectively [31,254]. Coincidently, study III showed that the patients' first biologic treatment was also commenced 11 years after the date of diagnosis. Therefore, from the perspective of preventing erosive progression and subsequently reducing the need for joint replacement surgery, it could be beneficial to initiate biologic treatment earlier in the course of RA as is currently recommended [7,8]. Whether this would be cost-effective is unclear and given the currently available evidence, any cost-effectiveness models on the subject would inevitably feature a considerable amount of uncertainty.

The incidence rate of revision operations was slightly higher among cDMARD users (IR 0.83 95% CI 0.68-1.02) as compared to biologic drugs users (IR 0.65 95% CI 0.46-0.89). The survival analyses on the need to perform a revision to a specific joint replacement installed prior to or during the follow-up period revealed no statistically significant differences. However, there was a trend favoring the bDMARD users and the plausible improvement in survival of prostheses would be in line with the reduced incidence rate of revision operations. The incidence rate of post-operative infections was similar between the treatment alternatives although it has been suspected that not all cases have been reported to FAR [255].

The pathologic process leading to aseptic loosening is largely driven by wear debris from the prosthesis, especially among patients with RA [149,256]. Also tumor necrosis factor alpha is involved in the process and it is suggested that bDMARDs could slow down the osteolytic process. Despite the lack of statistically significant difference in the incidence rate of revisions and survival stratified by joints, there was a tendency indicating that knee and hip revisions would be less common among biologic vs. synthetic DMARD users while the situation was reversed regarding other joints (Figure 8). The higher revision rate in cDMARD group compared to biologic drug users could perhaps reflect greater bone destruction or poorer bone quality at the time of primary surgery. However, owing to the role of inflammatory cytokines, such as TNF-α, in aseptic loosening and because they stimulate osteoclast activity, it could be speculated that the lower revision rates in the biologic users might be due to inhibition of the chronic foreign body inflammation (particle disease).

6.6 Limitations of the study

6.6.1 Limitations of the systematic review (I)

Our systematic review features several limitations that need to be taken into account when evaluating the implications of the results. The efficacy and safety results pooled in the meta-analysis derive from RCTs, which have been conducted as multi-center studies globally and may therefore not be directly generalizable to Finnish healthcare. The generalizability of the results may be further hampered by the stringent inclusion criteria, which often exclude patients with co-morbidities and prior biologic treatments [12,218]. Some of the studies included in the systematic review neglected to report the efficacy and safety results at all relevant time-points such as 3, 6 and 12 months after treatment onset despite sufficient trial length, resulting in decreased statistical power. We could have addressed this by contacting the authors of the original publications for unpublished data, but were unable to do so within the time constrain. Indirect comparison of TNF-blockers may be biased due to differences in the inclusion criteria, year of publication and the choice of comparator. We excluded all non-randomized studies as a classical frequentistic meta-analysis would probably not have been suitable to pool their results and hence, possibly ignored some information on the effectiveness and safety of TNF-inhibitors. A Bayesian meta-analysis with meta-regression on the other hand, could have addressed for the between-study differences and incorporated information from observational trials [257]. Undertaking one however, would have required considerably more expertise in statistics and statistical programming than that we possessed at the time.

6.6.2 Limitations of the cross-sectional study (II)

While a cross-sectional study was suitable for providing an overview on the prevalent disease activity and medical treatment, it did not warrant any causal conclusions as a longitudinal study design would have. The data for our study was gathered from six out of twenty Finnish hospital districts, which might limit the generalizability of the results to the rest of the country. Although the initial protocol called for an equal number of participants from each hospital district, this was not achieved. Also, the actual number of included patients was not proportional to the total population residing within the boundaries of each participating hospital district. Despite including consecutive patients without any additional inclusion criteria into the study, patients with high disease activity and hence, more frequent visits to rheumatologists, might be overrepresented. The questions on employment status and educational background were misinterpreted or omitted by many patients and consequently, we chose not to report the results on these.

6.6.3 Limitations of the cohort studies (III and IV)

Although the ROB-FIN covers an estimated 60% of the biologic treatments in rheumatic diseases, the unexposed cDMARD cohort was based only on the records of a single hospital district and therefore, the comparisons between the biologics and cDMARD users may have limited generalizability [227]. There were differences between the cDMARD populations used in the two analyses, however. The study focused on the incidence of joint replacement operations (IV) featured follow-up data from a longer period of time with limited data on disease activity and co-medication whereas the study on the incidence of serious infections and malignancies (III) used data from 2007 onwards based electronic reporting with more accurate information on possible confounders. Most of the data is gathered alongside daily clinical work where it is not always possible to write up information systematically. Missing data was evident in both analyses and had to be imputed in order to perform the multivariate analyses. Using multiple imputation however, we were able to conduct the analyses on all patients and account for the uncertainty caused by the missing data. A large proportion of patients were lost to follow-up, which may have introduced some bias into our results. Our data was not accurate enough to specify if the biologic treatment was halted shortly prior and after the joint replacement surgery. Prior joint replacement operations, serious infections and malignancies were used as confounding factors, but the data on joint replacement operations and serious infections were only available to us from 1980 and 1998 onwards, respectively. Therefore, we may have been able to account for them as confounders only partially. Propensity score matching used in the cohort study IV facilitates the analysis of the outcome of interest between two groups, but due to exclusion of unmatched patients, the results of the remaining participants in either of the treatment arms might no longer generalizable to the original population. We did not have information on all patients' co-morbidities, smoking status, educational background, erosive progression in weight bearing joints or medication adherence, all of which could potentially confound the results. Propensity score matching as well as any other statistical technique besides randomization can only account for differences in the measured variables between the treatment groups and ignores or even worsens the balance in unmeasured ones.

The data on infections were retrieved from hospital records, which only represent the most severe cases of infections. Serious infection is often in practice defined as one requiring hospitalization, whereas mild to moderate infections can usually be treated in the outpatient setting. While some infections such as sepsis are always likely to lead to hospitalization and the results might therefore represent their true incidence, the same cannot be said from bronchitis for example, which is usually treated in community health centers by general practitioners.

Lag-time in the cohort study on serious infections and malignancies (III) was longer compared to that used by some others [121,252]. This was in part motivated due to instructed data reporting interval of six months for ROB-FIN and the limitation of us not being able to define the medication period more accurately than as the time between two visits while on drug. Lag-time was not used in the cohort study on joint replacement operations (IV), which could have led to omission of operations taking place shortly after the biologic treatment is discontinued or the patient is lost to follow-up.

7 CONCLUSIONS

In the present study we sought to improve the knowledge on the efficacy, long-term outcomes and safety of biologic drugs in comparison to synthetic DMARDs.

I: Our results disclosed few differences between individual TNF-inhibitors regarding efficacy and safety based on the information available from randomized clinical trials. TNF-inhibitors are more efficacious when used in conjunction with methotrexate compared to biologic monotherapy. Our meta-analysis did not identify an increased risk for serious infections among biologics users compared to patients on synthetic DMARDs.

II: The cross sectional review of patients with RA revealed that >50% of patients were in DAS28-remission and 70% had low disease activity. Comparison to previous studies revealed a possible reduction in disease activity of prevalent RA. Of the included 890 patients, 21% and 91% were using biologic and synthetic DMARDs, respectively.

III: There were no statistically significant differences in the incidence of infections requiring hospitalization and malignancies between the users of cDMARDs, infliximab, etanercept, adalimumab or rituximab. However, it is possible that the present study was statistically underpowered. The study population covers a major proportion of Finnish RA patients ever exposed to biologic treatment and thus, is highly generalizable inside Finland. Generalization outside Finland however, is not recommended due to differences in treatment guidelines, population characteristics and comorbidities such as latent tuberculosis.

IV: We tested the assumption that the use of biologic drugs would diminish the need for joint replacement surgery in patients with RA. Contrary to our hypothesis the incidence rate of operations to joints other than hip was higher among biologics users, may be due to unmeasured differences in disease severity and erosive progression. Biologic anti-rheumatic drugs were not found to be associated with increased risk of infection. Despite possibly lower rate of revisions among biologic users, the durability of prostheses was not improved compared to DMARD users. It is possible that biologic drugs to a larger extent prevented from the need for joint replacement surgery if initiated earlier in the course of the disease. More research on the subject is needed and while a randomized controlled trial would provide the strongest evidence it may be not feasible considering the long-time span needed for follow-up.

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Appendix 1. Search strategy used for (Ovid) Medline.

Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process (5.2.2010)		
# ID	Search term	Search results
1	(rheumatoid adj1 arthritis).mp.	85757
2	tnf*.mp.	91740
3	tumo?r necrosis factor*.mp.	105378
4	antitnf*.mp.	22
5	anti-tnf*.mp.	4655
6	antitumo?r necrosis factor*.mp.	233
7	anti-tumo?r necrosis factor*.mp.	1724
8	(infliximab* or remicade* or cA2*).mp.	117680
9	(etanercept* or enbrel* or p75TNFR-Fc*).mp	2430
10	(adalimumab* or humira* or D2E7*).mp.	1456
11	(certolizumab* or cimzia* or CDP870*).mp.	173
12	(golimumab* or simponi* or CNTO-148*).mp.	56
13	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	238383
14	random*.mp.	630336
15	rct*.mp.	8095
16	((single* or double* or trebl* or tripl*) adj1 (blind* or mask*)).mp.	141997
17	placebo*.mp.	135062
18	(clinical adj trial*).mp.	644131
19	(meta adj1 analy*).mp.	41768
20	metaanaly*.mp.	1060
21	(systematic* adj3 (review* or overview* or litera* or search*)).mp	27972
22	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	1065142
23	1 and 13 and 22	1556

Appendix 2. Description of the studies included in the systematic review and meta-analysis

Study and additional publications	Intervention (I) and control groups (C)	No of patients	Disease duration (years)	No of swollen joints	No of tender joints	HAQ	Previous MTX use	MTX dose (mg/vk)	Primary clinical outcome	RCT duration
Abe 2006[49]	I_1: 3mg/kg Inf + MTX	49	9,1	15,1	19	n/a	Yes	7,1[2]	ACR 20	14 weeks
	I_2: 10mg/kg Inf+ MTX	51	7,1	13,2	18,7	n/a	Yes	7,1[2]	14wk	
	C_1: MTX + placebo	47	7,5	13,5	17,8	n/a	Yes	7,4[2]		
	Inf at weeks 0, 2 and 6									
Maini 1999[53]	I_1: Inf 3mg/kg+MTX e8w	86	10	22	32	1.8	Yes	16	ACR 20	30 weeks
Lipsky 2000[51]	I_2: Inf 3mg/kg+MTX e4w	86	9	21	31	1.7	Yes	16	30wk	
Maini 2004[52]	I_3: Inf 10mg/kg+MTX e8w	87	11	23	32	1.7	Yes	16		
Smolen 2005[56]	I_4: Inf 10mg/kg+MTX e4w	81	12	24	34	1.7	Yes	17		
	C_1: Placebo + MTX	88	11	21	31	1.7	Yes	16		
Quinn 2005[54]	I_1: Inf 3mg/kg+MTX	10	0,62	n/a	n/a	1,3	No	15	No clinical primary endpoints	12 months
	C_1: Placebo + MTX	10	0,5	n/a	n/a	1,3	No	19		
	Inf at weeks 0, 2 and 6, then every 8 weeks									
Schiff 2008[55]	I_1: Inf 3mg/kg + MTX	165	7,3	20,3	31,7	1,7	Yes	16,3	DAS 28 6kk (abatacept vs. infliximab)	12 months[5]
Bessette 2007[50]	C_1: Placebo + MTX	110	8,4	20,1	30,3	1,8	Yes	16,6		
Van Vollenhoven 2008[59]	*Inf at weeks 0, 2 and 6, then every 8 weeks*									
St. Clair 2004[58]	I_1: Inf 3mg/kg + MTX	359	0,8	21	32	1,5	No	15,5	ACR-N 54 wk	54 weeks
	I_2: Inf 10mg/kg + MTX	363	0,9	22	33	1,5	No	14,9		
Smolen 2006[57]	C_1: Placebo + MTX	282	0,9	22	34	1,5	No	15,1		
	Inf at weeks 0, 2 and 6, then every 8 weeks									
Bathon 2000[61]	I_1: 25mg Eta	207	1	24	31	n/a	No		ACR-N 0-6mo	12 months
Bathon 2003[60]	C_1: MTX + placebo	217	1	24	30	n/a	No	19		
Genovese 2002[64]	*Eta twice a week*									
Emery 2008[62]	I_1: Eta 50mg + MTX	274	0,733	17,1	25,1	1,7	No	16,8	DAS remission 52wk	52 weeks
Emery 2010[63]	C_1: MTX + placebo	268	0,775	17,6	24,8	1,6	No	19.6 (wk 8)		
	Eta once a week									
Keystone 2004[66]	I_1: Eta 50mg	214	9	19.2	26[3]	1,4	No/yes	14.3(53%)	ACR 20 8 wk	16 weeks
	I_2: Eta 25mg	153	8,2	19.2	29.2[3]	1,4	No/yes	15.0(52%)		
	C_1: Placebo	53	10,8	19.2	24.6[3]	1,4	No/yes	13.8(55%)		
	Some of the patients on MTX									
Klareskog 2004[67]	I_1: Eta 25mg	223	6,3	23,0	35	1.7	No/yes	16,9	ACR-N wk 24	52 weeks
Kavanaugh 2008[65]	I_2: Eta 25mg + MTX	231	6,8	22,1	34,2	1.8	No/yes	17,2		
Van der Heijde 2006[71]	C_1: Placebo + MTX	228	6,8	22,6	33,1	1.7	No/yes	(wk 8)		
Van der Heijde 2007[70]	*Eta twice a week*									
Lan 2004[68]	I_1: Eta 25mg + MTX	29	n/a	13,21[1]	14,03[1]	0,99	Yes	12,5-20	SJC and TJC	12 weeks
	C_1: Placebo + MTX	29	n/a	14.45[1]	16.00[1]	1,23	Yes	12,5-20		
	Eta twice a week									
Moreland 1999[69]	I_1: Eta 25mg	78	11	25	33	1,6	No/yes		ACR 20 and 50 3 and 6mo	6 months
	C_1: Placebo	80	12	25	35	1,7	No/yes			
	Eta twice 2 week									

(continued) Appendix 2. Description of the studies included in the systematic review and meta-analysis

Weinblatt 1999[72]	I_1: Eta 25mg + MTX C_1: Placebo + MTX *Eta twice a week*	59 30	13 13	20[4] 17[4]	28[4] 28[4]	1,5[4] 1,5[4]	Yes Yes	19 18	Endpoints not specified	24 weeks
Breedveld 2006[73]	I_1: Ada 40 mg + MTX I_2: Ada 40 mg + placebo C_1: MTX + placebo *Ada every other week*	274 268 257	0,7 0,7 0,8	21,8 21,1 22,1	31,8 30,7 32,3	1,6 1,5 1,5	No No No	0 16.3 16.9	ACR 50 12mo	2 years
Chen 2009[74]	I_1: Ada 40mg + MTX C_1: MTX + placebo *Ada every other week*	35 12	6,2 8,3	21,9 24,1	32,5 37,2	1,7 1,8	Yes Yes	10-15 10-15	ACR 20 12wk	12 weeks
Keystone 2004[77] Jamal 2009[75] Keystone 2003[76]	I_1: Ada 40mg + MTX C_1: Placebo + MTX *Ada every other week*	207 200	11 10,9	19,3 19,0	27,3 28,1	1,45 1,48	Yes Yes	16.7 16.7	ACR 20 wk 24 HAQ wk 54	52 weeks
Kim 2007[78]	I_1: Ada 40mg + MTX C_1: Placebo + MTX *Ada every other week*	65 63	6,8 6,9	12,2 12,8	19,2 20,3	1,4 1,3	Yes Yes	16,6[2] 16,3[2]	ACR 20 wk 24	24 weeks
Miyasaka 2008[79]	I_1: Ada 40mg I_2: Ada 80mg C_1: Placebo *Ada every other week*	91 87 87	9,9 9,5 8,4	19,1 20,8 19,3	24,4 24,9 23,7	1,64 1,77 1,39	No/yes No/yes No/yes		ACR 20 24wk	24 weeks
Van de Putte 2003[80]	I_1: Ada 40mg I_2: Ada 80mg C_1: Placebo *Ada every other week*	70 72 70	10 10,1 9,4	18,7 19,6 19,8	31,0 32,5 30,9	1,74 1,66 1,63	No/yes No/yes No/yes		ACR 20 12wk	12 weeks
Van de Putte 2004[81]	I_1: Ada 40mg *eow* I_2: Ada 40mg *weekly* C_1: Placebo	113 103 110	10,6 11,9 11,6	20,5 19,3 19,8	33,7 33,8 35,5	1,83 1,84 1,88	No/yes No/yes No/yes		ACR 20	26 weeks
Weinblatt 2003[82]	I_1: Ada 40mg + MTX I_2: Ada 80mg + MTX C_1: Placebo + MTX *Ada every other week*	67 73 62	12,2 12,8 11,1	17,3 17,0 16,9	28,0 30,3 28,7	1,55 1,55 1,64	Yes Yes Yes	16,4 17,2 16,5	ACR 20 24wk	24 weeks
Emery 2009[83]	I_1: Gol 100mg+placebo I_2: Gol 50mg+MTX I_3: Gol 100mg+MTX C_1: MTX + placebo *Gol every 4 weeks*	159 159 159 160	4.1 3.5 3.6 2.9	12 13 14 11	24,5 26 26 25,5	1,7 1,5 1,6 1,5	No No No No	 19,2 19,1 19,1 (wk 23)	ACR 50 24wk	52 weeks
Kay 2008[84]	I1: Gol 50mg+MTX (eow) I2: Gol 50mg+MTX (e4w) I3: Gol 100mg+MTX (eow) I4: Gol 100mg+MTX (e4w) C1: MTX + placebo	35 34 34 34 35	8,2 8,2 6,3 9,0 5,6	14 14 20 14 13	28 28 32 22 22	1,7 1,6 1,8 1,3 1,3	Yes Yes Yes Yes Yes	≥10 ≥10 ≥10 ≥10 ≥10	ACR 20 16wk	52 weeks
Keystone 2009[85]	I_1: Gol 100mg + placebo I_2: Gol 50mg + MTX I_3: Gol 100mg + MTX C_1: MTX + placebo *Gol every 4 weeks*	133 89 89 133	5,9 4,5 6,7 6,5	11 13 12 12	22 26 23 21	1,38 1,38 1,38 1,25	Yes Yes Yes Yes	15 15 15 15	ACR 20 wk 14	52 weeks
Fleischmann 2009[86]	I_1: Cer 400mg C_1: Placebo *Cer every 4 weeks*	111 109	8,7 10,4	21,2 19,9	29,6 28,3	1,4 1,6	No/yes No/yes		ACR 20 24wk	24 weeks

(continued) Appendix 2. Description of the studies included in the systematic review and meta-analysis

Keystone 2008[87]	I_1: Cer 200mg + MTX	393	6,1	21,7	30,8	1,7	Yes	13,6[2]	ACR 20 wk 24	52 weeks
	I_2: Cer 400mg + MTX	390	6,2	21,5	31,1	1,7	Yes	13,6[2]		
	C_1: MTX + placebo	199	6,2	21,2	29,8	1,7	Yes	13,4[2]		
	Cer every 2 weeks									
Smolen 2009[88]	I_1: Cer 200mg + MTX	246	6,1	20,5	30,1	1,6	Yes	12,5[2]	ACR 20 24wk	24 weeks
	I_2: Cer 400mg + MTX	246	6,5	21,0	30,0	1,6	Yes	12,6[2]		
	C_1: Placebo + MTX	127	5,6	21,9	30,4	1,6	Yes	12,2[2]		
	Cer every other week									

[1] = Evaluation based on 28 joints
[2] = Baseline data
[3] = Evaluation based on 71 joints
[4] = Values in median
[5]= placebo switched to active medication at 6 months

Ada = Adalimumab
Cer = Certolizumab pegol
Eta = Etanercept
Gol = Golimumab
Inf = Iinfliximab
MTX = methotrexate

ORIGINAL PUBLICATIONS