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A CLINICAL AND HEALTH ECONOMICAL OBSERVATIONAL STUDY OF ANTI-TUMOR NECROSIS FACTOR THERAPY IN THE TREATMENT OF RHEUMATOID ARTHRITIS IN FINLAND

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ACADEMIC DISSERTATION

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Contents

1 LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I. Nordstrom DC, Konttinen L, Korpela M, Tiippana-Kinnunen T, Eklund K, Forsberg S, Ilva K, Kaipiainen-Seppanen O, Malmi T, Yla-Kerttula T, Honkanen V. Classic disease modifying anti-rheumatic drugs (DMARDs) in combination with infliximab. The Finnish experience. Rheumatol Int. 2006;26(8):741-8.

II. Konttinen L, Honkanen V, Uotila T, Pollanen J, Waahtera M, Romu M, Puolakka K, Vasala M, Karjalainen A, Luukkainen R, Nordstrom DC, for the ROB-FIN study group. Biological treatment in rheumatic diseases: results from a longitudinal surveillance: adverse events. Rheumatol Int. 2006;26(10):916-22.

III. Virkki LM, Konttinen YT, Peltomaa R, Suontama K, Saario R, Immonen K, Jäntti J, Tuomiranta T, Nykänen P, Hämeenkorpi R, Heikkilä S, Isomäki P, Nordström D. Cost-effectiveness of infliximab in the treatment of rheumatoid arthritis in clinical practice. Clin Exp Rheumatol. 2008;26(6):1059-66.

IV. Virkki LM, Valleala H, Takakubo Y, Vuotila J, Relas H, Komulainen R, Koivuniemi R, Yli-Kerttula U, Mali M, Sihvonen S, Krogerus ML, Jukka E, Nyrhinen S, Konttinen YT, Nordström DC. Outcomes of switching anti-TNF drugs in rheumatoid arthritis--a study based on observational data from the Finnish Register of Biological Treatment (ROB-FIN). Clin Rheumatol. 2011;30(11):1447-54.

The studies are referred to in the text by their Roman numerals.

In addition, some unpublished results are presented (V).

2 ABBREVIATIONS

Ab	antibody
ACPA	anti-citrullinated protein antibody
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% improvement criteria
ACR50	American College of Rheumatology 50% improvement criteria
ACR70	American College of Rheumatology 70% improvement criteria
ADA	adalimumab
ADAb	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
anti-CCP	anti-cyclic citrullinated peptide
APC	antigen-presenting cell
bDMARD	biological disease modifying antirheumatic drug
CD	cluster of differentiation
CDAI	Clinical Disease Activity Index
CDC	complement-dependent cytotoxicity
cDMARD	conventional disease modifying antirheumatic drug
CER	certolizumab pegol
CI	confidence interval
CMC	carpometacarpal
COX	cyclooxygenase
CQG	cost per QALY gained
CRP	C-reactive protein
CUA	cost-utility analysis
CVD	cardiovascular disease
DAS	Disease Activity Score
DAS28	Disease Activity Score using 28 joint counts
DDD	defined daily dose
DIP	distal interphalangeal
DMARD	disease modifying antirheumatic drug
DNA	deoxyribonucleic acid
ERA	early rheumatoid arthritis
ESR	erythrocyte sedimentation rate
ETA	etanercept
EULAR	European League Against Rheumatism
Fc	fragment crystallizable (of an antibody)
FcγR	Fc-gamma receptor
FCR	Finnish Cancer Registry
FDA	U.S. Food and Drug Administration
FSM	Finnish Statistics on Medicines
GAG	glycosaminoglycan
GC	glucocorticoid
GOL	golimumab
HAQ	Health Assessment Questionnaire
HCQ	hydroxychloroquine
HLA	human leukocyte antigen
HR	hazard ratio

HRQOL	health-related quality of life
HRT	hormone replacement therapy
IFN-γ	interferon-gamma
IFX	infliximab
IgG	immunoglobulin G
IL	interleukin
i.v.	intravenous
JAK	janus kinase
JSN	joint-space narrowing
kDa	kilodalton
LDAS	low disease activity state
LEF	leflunomide
LOE	lack, or loss, of effectiveness
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MCP	metacarpophalangeal
MDA	minimal disease activity
MHC	major histocompatibility complex
MMP	matrix metalloproteinase
mRNA	messenger RNA
MTP	metatarsophalangeal
MTX	methotrexate
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NSAID	non-steroidal anti-inflammatory drug
OC	oral contraceptive
OR	odds ratio
PBO	placebo
PIP	proximal interphalangeal
PJC	painful joint count
pLOE	primary lack of effectiveness
QALY	quality-adjusted life year
RA	rheumatoid arthritis
RANKL	receptor activator of nuclear factor kappa-B ligand
RASF	rheumatoid arthritis synovial fibroblast
RCT	randomized controlled clinical trial
RF	rheumatoid factor
RNA	ribonucleic acid
ROB-FIN	Finnish register of biological treatment
RR	risk ratio
SAE	serious adverse event
s.c.	subcutaneous
SDAI	Simplified Disease Activity Index
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SII	Social Insurance Institution of Finland (Kansaneläkelaitos)
SIR	standardized incidence ratio
SJC	swollen joint count
SJC28	swollen joint count, 28 joint index
SJC54	swollen joint count, 54 joint index
sLOE	secondary lack (loss) of effectiveness
SLR	systematic literature review

SSZ	sulfasalazine
TB	tuberculosis
TJC	tender joint count
TJC28	tender joint count, 28 joint index
TJC53	tender joint count, 53 joint index
TLR	Toll-like receptor
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
TNFR	tumor necrosis factor receptor
TRAF2	TNF receptor-associated factor 2
ULN	upper limit of normal
VAS	visual analogue scale
vdH-S	van der Heijde modification of the Sharp radiographic scoring system
VEGF	vascular endothelial growth factor

3 ABSTRACT

The advent of biological drugs has significantly, even dramatically, improved the prognosis of rheumatoid arthritis (RA) in a substantial proportion of patients with moderate to severe active disease refractory to treatment with conventional disease modifying antirheumatic drugs. Anti-tumor necrosis factor (anti-TNF) agents were the first biologicals to emerge at the turn of the century, and they are still the most widely used among this group of drugs. The efficacy and safety of the biological drugs in RA and other rheumatological conditions for which they are approved have been evaluated in randomized controlled trials usually of three to twelve months duration with strict inclusion and exclusion criteria to define the study population.

To enable nationwide prospective, longitudinal follow-up of outcomes in adult patients with rheumatologic diseases treated with biological agents, the Finnish Society for Rheumatology established the Finnish register of biological treatment, ROB-FIN, in accordance with international recommendations. The observational data presented in this study indicates the effectiveness of infliximab and other anti-TNF agents in the treatment of (long-standing, methotrexate refractory) RA to be similar to the efficacy in randomized controlled trials, even though the settings are fundamentally different, e.g., in terms of patient selection (eligibility criteria and allocation to treatment), knowledge of the intervention (open-label *vs.* double-blind), and flexibility in the treatment strategy.

Anti-TNF therapy appeared to be well-tolerated in most patients. During a mean follow-up time of 2.1 years, adverse events (AEs) were reported in 17%, and led to discontinuation of the treatment in 9%, of the registered patients. The most common and treatment-limiting AEs comprised of various infections, eczemas and skin reactions, infusion or allergic reactions, various general symptoms, and laboratory abnormalities. Patients with RA appeared more susceptible to AEs than those with other rheumatological diagnoses (risk ratio 1.7, $p<0.001$). Serious, life-threatening, or fatal adverse events (SAEs, excluding cancer) were reported in 3.1% (fatal 0.2%) of the registered patients. The main cluster of SAEs comprised of diverse infections (reported in 1.8% of the registered patients). Cancer was diagnosed in 3.0% of RA patients during or after biological therapy. Compared with the Finnish general population, the overall incidence of cancer did not appear to be increased. Cases of skin melanoma and pharyngeal cancer were few, but their incidence rates were higher among the ROB-FIN cohort than among the Finnish general population. However, the confidence intervals are wide, and further studies would be required in order to more reliably assess these risks.

Switching to another biological drug was common and due to lack or loss of response, adverse drug reactions, and other reasons. The assessments of the outcomes of anti-TNF drug switching gave reason to suspect anti-drug antibodies as a potential contributor to reduced drug response. Anti-drug antibodies and serum drug concentrations are not routinely monitored currently, but have been increasingly identified as potentially valuable assessments in anti-TNF non-responders from both clinical and economical perspectives of therapeutic decision making.

An analysis relating the direct medical costs of infliximab to the change in health-related quality of life indicated that Finnish RA patients have been cost-effectively treated in terms of improvement in functional capacity and patient-reported assessment of disease activity.

In absolute terms the direct medical costs of anti-TNF and other biological agents are high, but several possibilities exist, or may come to exist, that might lower them and maximize the cost-effectiveness; these include the possible advent of biosimilars, the treat-to-target approach in the management of RA, and personalized medicine.

4 REVIEW OF THE LITERATURE

4.1 An overview of rheumatoid arthritis (RA)

4.1.1 Implications of RA for the patient and society

Rheumatoid arthritis (RA) is an autoimmune disease which, in its active form, is characterized by chronic polyarticular synovial inflammation and progressive joint damage. RA affects approximately 0.5–1% of the adult population worldwide (Firestein, 2003). In Finland, the prevalence has been estimated to be 0.8% (ca 40 000 patients); approximately two-thirds of the affected patients are women (Kaipiainen-Seppänen, 2004). Approximately 1600 patients are diagnosed with RA each year; the incidence seems to have declined over the past few decades (Kaipiainen-Seppänen, 2004; Kaipiainen-Seppänen and Kautiainen, 2006). Adult RA may start at any age, but the incidence peaks at the age of 55–65 years. Approximately two-thirds of the patients are at working age at the time of diagnosis (Puolakka *et al.*, 2010).

Articular symptoms of RA include swelling, tenderness, pain and morning stiffness. The most frequently affected joints are the wrists, metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, knees, ankles, elbows, shoulders and metatarsophalangeal (MTP) joints, and often the joints (or joint areas) are bilaterally affected (Tanaka *et al.*, 2005). Tenosynovitis and bursitis also occur. Rheumatoid inflammation is often accompanied with elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). The presentation and course of the disease vary greatly between patients (van Vollenhoven, 2011). Active, persistent rheumatoid inflammation causes tissue destruction in the articular cartilage, subchondral bone and periarticular soft tissues of the affected joints, and may ultimately lead to sequelae such as cervical spine disease and joint deformities (Rindfleisch and Muller, 2005).

RA is a heterogeneous, systemic disorder, with synovial inflammation being a major distinctive feature. Nonarticular manifestations may include fatigue, anemia, Felty's syndrome, pericarditis, pleuritis and certain pulmonary manifestations, subcutaneous nodules, cutaneous and other types of vasculitis, neuropathy, amyloidosis, glomerulonephritis, and various ocular manifestations (Moreland and Curtis, 2009). RA is also associated with comorbid conditions, such as atherosclerosis, cardiomyopathy, heart failure, myocardial infarction, stroke, osteopenia and osteoporosis, as well as with an increased risk of infections and lymphoproliferative malignancies (Mikuls, 2003; Rindfleisch and Muller, 2005; Moreland and Curtis, 2009). RA may also be associated with an increased prevalence of certain other autoimmune diseases, such as Hashimoto's thyroiditis (Somers *et al.*, 2006). Both intrinsic effects or features of RA (e.g., inflammatory pathways, reduced mobility, smoking) and iatrogenic effects may be involved in the development of the comorbid conditions (Mikuls, 2003; Rindfleisch and Muller, 2005). Peptic ulcer disease has been predominantly attributed to the usage of non-steroidal anti-inflammatory drugs (NSAIDs) (Mikuls, 2003).

RA and its comorbid conditions and complications predispose patients to premature or accelerated mortality (Mikuls, 2003). Patients are at increased risk of dying of cardiovascular diseases (CVDs), infections, cancers, and urogenital, gastrointestinal and

respiratory diseases (Sihvonen *et al.*, 2004). Deaths caused by RA declined during a period of study from 1971 to 1991 (Koivuniemi *et al.*, 2009).

The public health implications of RA are significant. RA is associated with reduced functional and working ability, resulting in a major economic and social burden (Puolakka *et al.*, 2004; Rat and Boissier, 2004; Strand and Khanna, 2010). Tight control of the disease requires multidisciplinary care and frequent, regular follow-up (Hakala *et al.*, 2009; Smolen *et al.*, 2010a). Moreover, 20–30% of patients of working age may become permanently work disabled within the first 2–3 years of the disease, and up to 50% within the first 10 years, despite treatment with disease modifying antirheumatic drugs (DMARDs) (Sokka *et al.*, 1999; Barrett *et al.*, 2000; Sokka, 2003; Sokka, 2009). Work capacity and productivity may be reduced also in the absence of permanent work disability (Puolakka *et al.*, 2004). The indirect costs of RA account for a significant proportion (up to three-fourths) of the total costs (Rat and Boissier, 2004). In addition to direct and indirect costs, RA is associated with significant "intangible costs" due to reduced quality of life, with, e.g., physical, emotional and social well-being being affected by the disease (Kirwan *et al.*, 2007; Laas *et al.*, 2009; Strand and Khanna, 2010; da Silva *et al.*, 2011).

4.1.2 Classification criteria

The diagnosis of RA is based on symptoms, symptom duration, physical examination, acute phase reactants, and serological tests. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have published classification criteria (Aletaha *et al.*, 2010a; Aletaha *et al.*, 2010b), which may be used as a diagnostic aid. However, the fundamental purpose of these criteria is to provide a uniform set of standards by which to evaluate whether an individual newly presenting with undifferentiated inflammatory synovitis is likely to develop persistent and/or erosive RA (for patients with a long-standing disease, the classification can be done based on the retrospectively available data). The criteria are intended for classification in clinical research and trials, and may help to identify those patients who are most likely to benefit from early initiation of DMARD therapy. The assessment of criteria fulfillment may be applied only if the patient has at least one joint with a definite clinical synovitis (swelling), which is not better explained by any other disease. A score-based algorithm is used; the scores from four categories (A-D) are added, and a score of ≥6/10 is needed for classification as definite RA. The categories and their scorings are as follows (further details are given in the original publications):

A) Joint involvement (swelling or tenderness; distal interphalangeal (DIP) joints, first carpometacarpal (CMC) joints and first MTP joints are excluded from the assessment)
   - one large joint (shoulder, elbow, hip, knee or ankle): 0
   - 2 to 10 large joints: 1
   - 1-3 small joints (MCP joints, PIP joints, second to fifth MTP joints, thumb interphalangeal joints, wrists; with or without involvement of large joints): 2
   - 4-10 small joints (with or without involvement of large joints): 3
   - > 10 joints (at least 1 small joint): 5

B) Serology (international unit values; negative: ≤ upper limit of normal (ULN); low-positive: >ULN, but ≤ 3×ULN; high-positive: > 3×ULN)

- negative rheumatoid factor (RF) and negative anti-citrullinated protein antibody (ACPA): 0
- low-positive RF or low-positive ACPA: 2
- high-positive RF or high-positive ACPA: 3

C) Acute-phase reactants (normal/abnormal is determined by local laboratory standards)
- normal CRP and normal ESR: 0
- abnormal CRP or abnormal ESR: 1

D) Duration of symptoms (patient's self-report of the maximum duration of signs or symptoms of synovitis (pain, swelling, tenderness) of any joint that is clinically involved at the time of assessment)
- <6 weeks: 0
- ≥6 weeks: 1

These criteria have replaced the 1987 American College of Rheumatology criteria, which are as follows (Arnett *et al.*, 1988, traditional format):

For classification as RA, at least four of the following seven criteria have to be fulfilled. Criteria 1-4 must have been present for at least six weeks.

1. Morning stiffness in and around the joints lasting ≥ 1 hour before maximal improvement
2. Arthritis of three or more joint areas simultaneously (soft tissue swelling or fluid observed by a physician). The 14 possible joint areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP.
3. Arthritis of hand joints (swelling in a wrist, MCP, and/or PIP joint)
4. Symmetric arthritis (simultaneous involvement of the same joint areas on both sides of the body, possible joint areas being those defined in the second criterion; bilateral involvement of PIPs, MCPs or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules (subcutaneous nodules in specific places, observed by a physician)
6. Serum rheumatoid factor, demonstrated by any method which gives a positive result for <5% of normal control subjects
7. Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs (erosions or unequivocal bony decalcification; osteoarthritis changes alone do not qualify).

The 1987 criteria replaced the 1956 American Rheumatism Association (ARA) diagnostic criteria, and have been used extensively in clinical trials (including those on tumor necrosis factor inhibitors (TNFi) and other biological agents) performed over the last couple of decades. The need to develop new criteria arose essentially from the changes in the management of RA during this period (Cohen and Emery, 2010). It had been recognized that early and effective intervention was essential in order to slow down the disease progression and prevent functional decline. Furthermore, new treatment options had become available by the turn of the century (including TNFi agents), and the diagnostic importance of ACPAs had become clear. Because of the recognized importance of early diagnosis, the roles of radiographic imaging and rheumatoid nodules have been downplayed in the new criteria, although radiographs of the hands and feet are usually taken during the initial diagnostic evaluation.

4.1.3 Pathogenesis of RA

The pathogenesis of RA is complex and not entirely known, especially regarding the initiating events which lead to the development of the disease. A genetic predisposal seems to be of importance (O'Hanlon *et al.*, 2011). In cross-sectional studies, concordance rates for RA have been found to be about 15% in monozygotic twins, compared to about 3.5% in dizygotic twins (Aho *et al.*, 1986; Silman *et al.*, 1993). One well-known genetic risk factor for disease susceptibility and/or disease severity are the alleles of the human leukocyte antigen (HLA) -DRB1 gene that encode for the so called "shared epitope" of the HLA-DRβ chain (a part of a major histocompatibility complex (MHC) class II cell surface receptor, which is necessary for binding and presentation of antigenic epitopes) (Ling *et al.*, 2007). However, in the disease onset the gene environment probably acts together with environmental risk factors.

Possible predisposing environmental factors include cigarette smoking and air pollutants, viral or bacterial agents, and heavy coffee consumption (Pedersen *et al.*, 2007; Münz *et al.*, 2009; Hoovestol and Mikuls, 2011). It has been proposed but not proven that protective factors include antioxidants, vitamin D and moderate alcohol intake.

It is known that gonadal (estrogens, progesterone, androgens) and adrenal (corticosteroids, dehydroepiandrosterone) hormones have immunomodulatory properties (Kanik and Wilder, 2000; Doran *et al.*, 2004; Nalbandian and Kovats, 2005; Forsblad d'Elia and Carlsten, 2008). RA is a female predominant disease (female/male incidence ratio being 5:1 in young adults, but 1:1 after the age of 60 years), with the highest incidence in females coinciding with menopause (Forsblad d'Elia *et al.*, 2003; Doran *et al.*, 2004; Forsblad d'Elia and Carlsten, 2008; Islander *et al.*, 2011). Moreover, pregnancy may suppress RA onset or activity, while the postpartum period is associated with an increased risk of RA development or flare (Kanik and Wilder, 2000; Forsblad d'Elia *et al.*, 2003; Doran *et al.*, 2004). Results from studies concerning the effects of oral contraceptives (OCs) or hormone replacement therapy (HRT) on the risk of RA have been conflicting (Doran *et al.*, 2004; Pedersen *et al.*, 2007; Hoovestol and Mikuls, 2011). Some studies indicate that OCs protect against the development of RA, while HRT may ameliorate RA inflammation and have beneficial effects on disease activity, bone mineral density and radiological disease progression (Brennan *et al.*, 1997; Forsblad d'Elia *et al.*, 2003; Doran *et al.*, 2004).

Rheumatoid factor (RF, a group of autoantibodies with anti-IgG specificity) and antibodies to citrullinated protein antigens (ACPAs) may be formed already in the subclinical phase of RA (Aho *et al.*, 1985; Bridges, 2004; van Vollenhoven, 2011). According to an etiologic hypothesis, an environmental agent, e.g. from smoking, may render self-molecules immunogenic by causing citrullination of proteins (Klareskog *et al.*, 2006); this modification may increase their affinity to the shared epitope, which may elicit $CD4^+$ T cell responses (Hill *et al.*, 2003). Although this particular set of events may not explain all the pathogenetic cascades of RA, it demonstrates the interplay between genes, environmental exposures and autoimmune reactions. Interestingly, immune complexes containing citrullinated fibrinogen have been found to effectively act on Toll-like receptor-4 (TLR-4) and Fcγ receptor (FcγR) and thereby to stimulate TNF production in macrophages (Sokolove *et al.*, 2011). Local inflammation in the synovium could lead to formation of citrullinated fibrinogen and consequent generation of ACPA and formation of immune complexes between these, which could amplify synovitis.

In addition to citrullinated protein targets, many other autoantigens have been implied in the pathogenesis of RA (Bläß *et al.*, 1999). Initiating antigens may be distinct from perpetuating ones (Li *et al.*, 2002; Firestein, 2005). Antigen presentation by professional antigen-presenting cells (APCs, i.e. dendritic cells, macrophages and B cells) involves the capture, transport, and processing of an antigen and then binding of its antigenic determinants (epitopes) to a MHC class II molecule in the endolysosomal compartment, and finally expression of the MHC class II – epitope complex on the surface of the APC (Firestein, 2005; Panayi, 2005). The MHC-antigen complex may then bind to a complementary T cell receptor. This, together with co-stimulatory signals (induced in part by danger-associated molecular patterns), e.g., ligation of a CD80/CD86 molecule on the APC with a CD28 molecule on the T cell, leads to T cell activation and clonal expansion in lymph nodes (Firestein, 2005).

The T cells in RA seem to predominantly differentiate into Type 1 (Th1) or Type 17 (Th17) helper T cells which, after migration to the synovium, act in several ways to coordinate the synovial inflammation. Th1 cells produce small amounts of the cytokine interferon-γ (IFN-γ), which, in turn, increases MHC class II expression and primes macrophages to produce inflammatory and tissue-damaging mediators, such as TNF-α, proteinases, reactive oxygen species and nitric oxide (Ma *et al.*, 2003; Firestein, 2005). Th17 cells and mast cells produce the cytokine interleukin-17 (IL-17, in particular IL-17A and also IL-17F), leading to increased levels of proinflammatory cytokines (including TNF-α, IL-1β, IL-6, and granulocyte macrophage colony-stimulating factor (GM-CSF), e.g., from macrophages and various stromal cells), adhesion molecules and matrix metalloproteinases (MMPs), as well as stimulation of osteoclastogenesis via induction of receptor activator of nuclear factor kappa-B ligand (RANKL) (Jovanovic *et al.*, 1998; Firestein, 2005; Brennan and McInnes, 2008; Moreland and Curtis, 2009; Hueber *et al.*, 2010; Waite and Skokos, 2012). In addition, activated T cells activate or interact with other cells that sustain the inflammation and joint destruction: B cells, macrophages, dendritic cells, neutrophils, mast cells, fibroblasts, lining cells, mesenchymal stromal cells, endothelial cells, neural cells, chondrocytes, osteoblasts, osteocytes and osteoclasts (Firestein, 2005). Some of the main events and key players in the pathogenesis of RA are depicted in Figure 1.

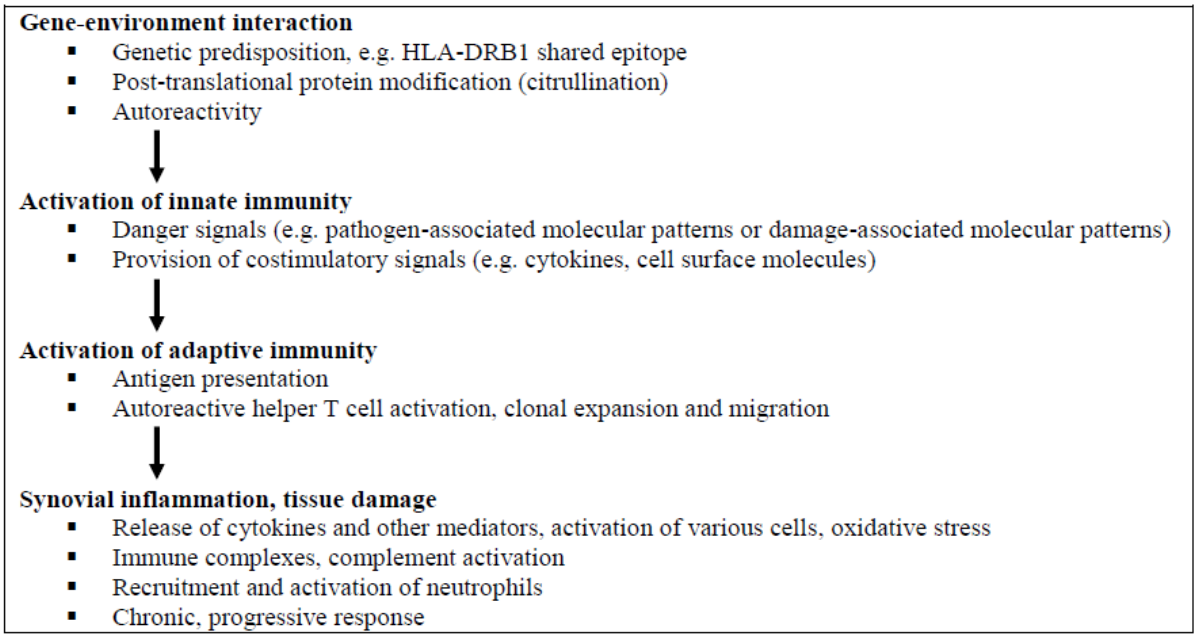

Figure 1. Main events and key players in the pathogenesis of RA.

B cells activated to plasma cells produce RF and other autoantibodies for export, which form immune complexes with the antigens which stimulated their production (Panayi, 2005). This leads to complement activation and subsequent recruitment of neutrophils and macrophages. Macrophages can be activated in several ways: by T cell contact or T cell derived cytokines (e.g., IFN-γ, IL-17), by immune complexes which trigger activating FcγR signalling, and by innate immune receptors stimulated with danger signals via, e.g., TLRs (Bingham, 2002; Sokolove *et al.*, 2011). The accumulation and persistent activation of macrophages has been found to correlate with the articular signs and symptoms of RA (Tak, 2005).

Oxidative stress can cause mutations in, e.g., the p53 tumor suppressor gene, leading to increased synoviocyte proliferation (Tak *et al.*, 2000). Furthermore, activation of RA synovial fibroblasts (RASFs) may occur already early in the disease process, e.g. through interaction of TLRs of the innate immune system with danger signals (Huber *et al.*, 2006). This activation leads to up-regulation of integrins, which enable the fibroblasts to adhere to and migrate along the extracellular matrix of the articular cartilage (i.e., collagen type II and cartilage glycosaminoglycans, GAGs). Subsequently, the expression of MMPs, cathepsins and proto-oncogenes is increased. RASFs also express RANKL which enhances the differentiation and fusion of macrophage-lineage osteoclast progenitors into multinuclear osteoclasts. In addition, RASFs produce pro-angiogenic factors and a variety of chemokines and cytokines. Moreover, apoptosis signalling is impaired in RASFs and synovial macrophages. These changes, in concert with other disease processes, lead to several interconnected pathophysiological phenomena: synovial hyperplasia, angiogenesis, attraction and accumulation of immune cells to the synovium, spreading and invasion of inflamed synovial and pannus tissue, and progressive destruction of articular cartilage, bone and periarticular soft tissues (Ainola *et al.*, 2005; Huber *et al.*, 2006).

Rheumatoid synovial tissue is characterized by intimal lining hyperplasia, increased vascularity and an accumulation of cells in the synovial sublining: dendritic cells, T cells, macrophages, B cells, plasma cells, neutrophils, mast cells and natural killer cells (Tak, 2005; Ahern and Brennan, 2011), even organized into secondary lymphatic follicles, which represent the morphological equivalent of the T cell-dependent, B cell-mediated immunoglobulin synthesis usually seen in secondary lymphatic tissues (Konttinen *et al.*, 1981). Pro-inflammatory cytokines, e.g., TNF, IL-1, IL-6 and IL-17, are central mediators in processes leading to articular symptoms and damage. They may also be involved in some of the systemic manifestations, e.g. anaemia, fatigue, generalized bone loss and cardiovascular disease (atherosclerosis, myocardial infarction, coronary artery disease), although other causes have been recognized as well (Moreland and Curtis, 2009).

4.2 Evaluating drug effects in RA

4.2.1 Randomized controlled trials, clinical trials and observational studies

A clinical trial is a procedure in medical research with the aim of collecting data on the efficacy and safety of health interventions. Clinical trials, e.g. of new treatment modalities, may be required prior to gaining marketing authorization. A randomized controlled clinical trial (RCT) is a type of clinical trial in which study subjects are allocated to their respective intervention in an unpredictable sequence to minimize allocation bias, and the outcomes of the study intervention(s) are compared with a control intervention. Well designed and properly conducted RCTs provide solid evidence of the study intervention regarding its safety and efficacy, i.e., the capacity to produce the intended effect. This may necessitate application of strict inclusion and exclusion criteria to define the study sample, which narrows down the patient population to a distinctly selected group of patients. For example, it has been estimated that less than one-third, even less than one-tenth, of RA patients starting TNFi therapy in clinical practice would fulfil the inclusion and exclusion criteria which have been used in the clinical trials of TNFi drugs (Kvien *et al.*, 2003; Zink *et al.*, 2006). Furthermore, patients and investigators participating in RCTs may be particularly committed to the trial and trial drug. These, and other factors (such as geographical area in which the study is conducted), may lead to a limitation of the external validity, i.e., generalizability, of the RCT results.

Observational studies can have a case-control (retrospective) or cohort (prospective) design. They can complement RCTs by providing information on effectiveness, i.e., the extent to which a treatment modality achieves its intended effect in the usual clinical setting, and safety, including long-term and rare events (Marley, 2000; Silverman, 2009). The follow-up of patients with chronic conditions may be significantly longer in observational studies, compared with the often relatively short duration (e.g. weeks or months) of an RCT. Methodological limitations of observational studies include selection bias due to the non-randomized setting (confounding by indication), and incompleteness of the data due to, e.g., the available data being limited to that included in the data source; incomplete or under-reporting; and patients being lost to follow-up in the long-term (Sokka, 2009).

4.2.2 Assessment of disease status and outcomes of pharmacological therapy

The individual clinical response to DMARD therapy is variable. Therefore, there is a need to quantify the response to treatment, both in clinical trials and routine practice. Various measures of disease activity have been published since the 1940s (Ranganath *et al.*, 2006). The first approach to classification of the response in clinical trials was based on the definition of a complete remission, with the American Rheumatism Association RA remission criteria being published in 1981 (Pinals *et al.*, 1981; Hider *et al.*, 2005). However, complete remission is seldom achieved (even with contemporary therapies), and therefore, criteria to identify patients achieving a sufficient improvement have been developed subsequently. The American College of Rheumatology (ACR) improvement criteria (Felson *et al.*, 1995) and the European League Against Rheumatism (EULAR) response criteria (van Gestel *et al.*, 1996) have gained the most widespread use. However, new remission criteria have recently been defined and are recommended for clinical trials (Felson *et al.*, 2011a; Felson *et al.*, 2011b).

The ACR criteria were developed based on a relatively widely internationally agreed core set of measures recommended for all RA clinical trials (Felson *et al.*, 1993; Felson *et al.*, 1995). The aim was to develop a single primary efficacy measure. First, baseline and post-treatment data on the core set of measures obtained from trials was compared with the impression of the rheumatologists of the improvement. This was done to reduce the initial number of candidate definitions of improvement. The remaining definitions were then tested on datasets from placebo-controlled DMARD trials to find those measures that maximally distinguished between effective and placebo treatments and minimized placebo response rates. In addition, attention was paid to the ease of their practical use. The finally selected definition of improvement is known as the ACR20. ACR20 response is achieved when the patient has at least 20% improvement in the swollen joint count (SJC) and the tender joint count (TJC), and in at least three of the five remaining ACR core set measures, i.e. patient and physician global assessments, pain score, physical function and an acute-phase reactant. In practice, improvement in excess of 20% is usually desired, and therefore usually also ACR50 (50% improvement) and ACR70 (70% improvement) response rates are reported. The ACR core set of measures can also be used to calculate numeric ACR (ACR-N), which is the lowest percentage change in the following three measures: SJC, TJC, and the median of the other five measures in the ACR core set (Siegel and Zhen, 2005). They can also be used to determine the proportion of patients achieving a satisfactory state of minimal disease activity (MDA, originally named low disease activity state, LDAS) (Wells *et al.*, 2006).

The EULAR response criteria are based on the Disease Activity Score (DAS) (van der Heijde *et al.*, 1990; van der Heijde *et al.*, 1993; van Gestel *et al.*, 1996). The DAS is a composite measure of disease activity obtained through statistical techniques applied on the decisions of rheumatologists to start treatment with DMARDs in patients with early RA. The DAS28 modification of the more complex original DAS has gained widespread use, and incorporates the 28-joint swollen and tender joint counts, ESR and the patient global assessment (Prevoo *et al.*, 1995; van Gestel *et al.*, 1998). Other modifications of the DAS and DAS28 provide options for different circumstances and include formulas which incorporate CRP instead of ESR and/or which omit the patient global assessment, as well as the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index

(CDAI) (Aletaha and Smolen, 2005). Using the EULAR response criteria, patients can be classified as good, moderate or non-responders according to the change in the DAS or DAS28 and the level of residual disease activity. Using the DAS28, the EULAR response criteria are as follows:

- current DAS28 ≤ 3.2 (indicating low disease activity) and
  - decrease in DAS28 > 1.2: good
  - decrease in DAS28 > 0.6 and ≤ 1.2: moderate
  - decrease in DAS28 ≤ 0.6: none
- current DAS28 > 3.2 and ≤ 5.1 and
  - decrease in DAS28 > 0.6: moderate
  - decrease in DAS28 ≤ 0.6: none
- current DAS28 > 5.1 (indicating high disease activity) and
  - decrease in DAS28 > 1.2: moderate
  - decrease in DAS28 ≤ 1.2: none

The question of whether an achieved response is considered "satisfactory" can be examined from the viewpoint of the physician's decision to stop or continue the DMARD, such decisions, however, being context and patient specific (e.g., dependent on the available treatment options and eventual side effects) (Hider *et al.*, 2005; Ranganath *et al.*, 2006).

RA sequelae and the efficacy or effectiveness of pharmacological therapy can also be evaluated radiographically, especially in long-term studies (e.g., beyond six to twelve months). Radiographs provide a rather permanent measure of damage that can be evaluated serially, and that does not fluctuate with disease activity (Scott *et al.*, 1997; Sokka, 2008). In clinical studies, an advantage is also that they can be evaluated in a randomized, blinded manner (Boini and Guillemin, 2001). Quantitative methods of assessment include the Larsen and Sharp scoring methods and modifications thereof, e.g., the van der Heijde modification of the Sharp erosion score. The contemporary scoring methods consider pre-specified joint areas in the hands, wrists and feet. Sharp methods involve separate scores for erosions and joint space narrowing, while Larsen methods give an overall score; the total scores have a continuous scale of more than 100 units, and the minimal clinically important difference is ca 1% of the maximum score (Sokka, 2008). The Larsen and Sharp scores correlate significantly, and the choice of scoring method depends on the required degree of reliability and sensitivity to change, and the time available for the assessments (Boini and Guillemin, 2001; Sokka, 2008).

Patient-reported outcome measures of health-related quality of life (HRQOL) are further recommended efficacy assessments for RA clinical trials (Smolen *et al.*, 2011). The choice of instrument depends on the specific purpose of the study. The instrument can be generic, such as the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36); EuroQol (EQ-5D); and 15D; or disease-specific, such as the Stanford Health Assessment Questionnaire (HAQ); Rheumatoid Arthritis Quality of Life Scale (RAQoL); and Arthritis Impact Measurement Scales (AIMS) (Carr, 2003; Linde *et al.*, 2008; Smolen *et al.*, 2011) (Table 1).

Table 1. Health-related quality of life (HRQOL) instruments used in RA outcome studies.

HRQOL instrument	Use	Dimensions of health/functioning
SF-36	Generic	Physical functioning; role limitations due to physical problems; bodily pain; social functioning; mental health; role limitations due to emotional problems; vitality; general health
EQ-5D	Generic*	Mobility; self-care; usual activities; pain/discomfort; anxiety/depression
15D	Generic*	Mobility; vision; hearing; breathing; sleeping; eating; speech/communication; excretion; usual activities; mental function; discomfort and symptoms; depression; distress; vitality; sexual activity
HAQ	Disease-specific (assessment of functional disability)	Dressing; arising; eating; walking; hygiene; reach; grip; usual activities
RAQoL	Disease-specific	Physical, emotional, and social limitations
AIMS	Disease-specific	Mobility; physical activity; dexterity; household activity; social activities; activities of daily living; pain; depression; anxiety

*) Utility measures for the assessment of patients' preferences for health states (applicable to pharmacoeconomical cost-utility analyses)

Safety monitoring during DMARD therapy is aided by, e.g., Summaries of Product Characteristics (SPC), and guidelines issued by local hospitals or national or international professional organizations (Saag *et al.*, 2008; Hakala *et al.*, 2009; Pham *et al.*, 2011; Singh *et al.*, 2012).

4.3 Treatment of RA, with focus on pharmacotherapy

4.3.1 Symptomatic and disease modifying antirheumatic drugs

Treatment with NSAIDs is a central component of pain management in RA (Schnitzer and Hochberg, 2002). The NSAIDs are a chemically heterogeneous group of drugs, whose principal mechanism of action is inhibition of prostanoid synthesis, by inhibition of cyclooxygenase (COX) enzymes (COX-1 and COX-2 in the case of nonselective NSAIDs, and COX-2 in the case of "coxib NSAIDs", i.e., COX-2 selective inhibitors) (Pelkonen and Ruskoaho, 2003). This results in their antipyretic effect and inhibition of platelet aggregation and is, at least partly, responsible for their anti-inflammatory and analgesic effects. The therapeutic effects of various NSAIDs are similar, but their pharmacokinetic characteristics differ. Long-term usage of nonselective NSAIDs, especially at high doses in susceptible patients, may lead to NSAID gastropathy, e.g., to peptic ulceration. Susceptibility to peptic ulceration is increased in those of age 65 years or more, who have had prior peptic ulcer disease or who use concomitant glucocorticoid (GC) or anticoagulant therapy (Schnitzer and Hochberg, 2002). Other serious adverse drug reactions of NSAIDs include nephrotoxicity and worsening of asthma (Pelkonen and Ruskoaho, 2003). Weak oral opioid analgesics (e.g., codeine, tramadol) are also effective for the treatment of pain in RA, at least in the short term (up to six weeks); however, side effects are common, which limits their utility (Whittle *et al.*, 2011).

Synthetic GCs are highly effective in quickly reducing inflammation and pain (Pelkonen and Ruskoaho, 2003). They affect the inflammatory processes in many ways, primarily by regulating the synthesis of proteins through regulation of the gene activity (directly or via transcription factors) or the rate of messenger RNA (mRNA) degradation. Importantly, they reduce the synthesis of inflammatory mediators and regulate the synthesis of enzymes involved in their production, leading to reduced levels of, e.g., prostanoids, cytokines (e.g., TNF, IL-1), nitric oxide, free radicals, bradykinin and tachykinins (e.g., substance P). In addition, they inhibit many inflammatory cell functions, such as synthesis of adhesion molecules in endothelial cells, neutrophil chemotaxis, histamine release from basophils, leukocyte movement and lymphocyte proliferation, ultimately leading to a reduction of inflammatory cell accumulation to the site of inflammation. GCs may increase the susceptibility, and complicate the recognition of, infections, and impede with wound healing and metabolic processes. These adverse effects limit long-term systemic usage, especially at moderate or high doses. Recently, modified-release GCs have been launched to relieve morning stiffness by mimicking the normal circadian rhythm of the hypothalamic-pituitary-adrenal axis and of the cortisol production (Buttgereit *et al.*, 2008; Buttgereit, 2011).

DMARDs are disease modifying in that they modify the immune system so that inflammation is suppressed and disease progression is slowed down. Conventional DMARDs (cDMARDs) include methotrexate (MTX), sulfasalazine (SSZ), chloroquine derivatives (hydroxychloroquine (HCQ), chroloquine), leflunomide (LEF), gold salts (sodium aurothiomalate, auranofin), cyclosporine, penicillamine, and cytostatic drugs (azathioprine, chlorambucil, cyclophosphamide) (Pelkonen and Ruskoaho, 2003). The exact pharmacodynamic mechanisms of most cDMARDs are not known. However, they have various, partially overlapping effects on inflammatory cells or mediators, which may explain their anti-inflammatory and antirheumatic effects. In general, it takes several weeks for the eventual clinical effect to take place. SSZ and LEF have been developed specifically for the treatment of RA, while for most of the other drugs, an antirheumatic effect has been found by chance. The main known pharmacodynamic effects of the most common cDMARDs in the treatment of RA are described briefly in Table 2.

Table 2. Features and pharmacodynamic effects of cDMARDs in the treatment of RA.

Drug name and features	Effects (in RA)	References
MTX ▪ Antineoplastic agent	▪ Inhibits the metabolism of folic acid ▪ In RA, low-dose MTX reduces cell-mediated immune responses and the production/effects of RF (but not ACPA) and various pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF) ▪ Increases the synthesis of the anti-inflammatory agent adenosine ▪ May inhibit arachidonic acid metabolism and rapid proliferation of cells (lymphocytes) in the synovium.	Bannwarth *et al.*, 1994 Pelkonen and Ruskoaho, 2003 Spadaro and Riccieri, 2005
SSZ ▪ A combination of the sulfonamide antibiotic sulfapyridine and the anti-inflammatory agent 5-aminosalicylic acid (5-ASA, i.e. mesalazine)	▪ SSZ may inhibit lymphocyte proliferation, the production of immunoglobulins (e.g., RF) and various cytokines (e.g., TNF), and the actions of neutrophils, and increase the release of adenosine ▪ Sulfapyridine may affect the angiogenic process of the inflamed synovium by reducing endothelial cell proliferation	Pullar *et al.*, 1985 Box and Pullar, 1997 Pelkonen and Ruskoaho, 2003
HCQ ▪ Mild immunosuppressant	▪ Stabilizes lysosomal membranes (prevents release of degradative enzymes) ▪ Raises intra-lysosomal pH, which interferes with several protein processing events and ultimately, e.g., reduces RF levels and lymphocyte proliferation ▪ May inhibit antigen presentation, intracellular TLRs, prostanoid and leukotriene synthesis and free-radical damage	Meng *et al.*, 2000 Pelkonen and Ruskoaho, 2003 Smolen *et al.*, 2010a Katz and Russell, 2011
LEF ▪ Active metabolite (A771726)	▪ Inhibits the enzyme dihydroorotate dehydrogenase (DHODH), which leads to reduced proliferation of activated lymphocytes ▪ Reduces the synthesis of cytokines, free radicals and immunoglobulins	Greene *et al.*, 1995 Pelkonen and Ruskoaho, 2003
Gold salts ▪ Injectable sodium aurothiomalate ▪ Oral auranofin	▪ Seem to inhibit the actions of degradative enzymes and complement; the synthesis of prostaglandins, leukotrienes and IL-1 and the formation of oxygen radicals; and lymphocyte proliferation, chemotaxis and phagocytosis by neutrophils	Pelkonen and Ruskoaho, 2003 Kean and Kean, 2008
Cyclosporine	▪ Binds to the cytosolic protein cyclophilin, which inhibits calcineurin and IL-2 production by activated T lymphocytes ▪ Also regulates other cell mediated reactions, e.g., by increasing transforming growth factor-beta (TGF-β) and IL-10 synthesis; decreasing vascular endothelial growth factor (VEGF) secretion; decreasing IL-15 and TNF production in fibroblasts; and impairing neutrophil chemotaxis	Lorenz, 2003
Azathioprine ▪ Active metabolites (6-mercaptopurine and purine thioanalogues) ▪ Purine antimetabolites	▪ Inhibit the synthesis of purine nucleotides and interfere with deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) biosynthesis and function ▪ Ultimately inhibit cell (lymphocyte) proliferation	Gaffney and Scott, 1998 Pelkonen and Ruskoaho, 2003

The biological DMARDs (bDMARDs) are produced with recombinant DNA technology and are specifically designed to block key mediators of the RA inflammatory process (Hider *et al.*, 2005). The first bDMARDs to emerge were TNFi agents, the first of which were licensed and approved for the treatment of RA around the year 2000. TNFi agents for human use were actually initially developed for treatment of a septic shock, but proved, in

clinical trials, to be ineffective or even detrimental (Abraham *et al.*, 1995; Fisher *et al.*, 1996; Clark *et al.*, 1998). However, by that time (early 1990s), critical preclinical experiments had provided a strong rationale for testing TNFi therapy also in human RA (Feldmann and Maini, 2001).

Currently (2013), five TNFi agents are in clinical use in Finland: infliximab (IFX; licensed 1999), etanercept (ETA; 2000), adalimumab (ADA; 2003), certolizumab pegol (CER; 2009) and golimumab (GOL; 2009). Details about their structures and features are presented in Table 3.

Table 3. Anti-TNF agents and their structures and features.

Anti-TNF agent	Structure and features	References
IFX	▪ Chimeric anti-TNF-α mAb[1], with a human IgG_1 constant (Fc) region[2] and murine variable (Fv) epitope-binding region ▪ The presence of the murine component may lead to production of HACAs; however, concomitant MTX use reduces the incidence of these	Arend, 2002 Maini and Feldmann, 2002 Anderson, 2005 Horiuchi *et al.*, 2010
ADA	▪ Fully human anti-TNF-α mAb	Kempeni, 1999
GOL	▪ Fully human anti-TNF-α mAb	Tak and Kalden, 2011
ETA	▪ Soluble TNF-α receptor (sTNFR), consisting of two extracellular ligand-binding domains of the human 75 kDa TNF type 2 receptor, linked to a Fc region of human IgG_1 ▪ The dimeric receptor has a greater affinity for TNF-α than the naturally occurring monomeric sTNFR ▪ The linkage to the Fc region provides the construct with better retention (longer half-life) in the circulation ▪ Also binds and neutralizes lymphotoxin-α (TNF-β) ▪ Compared to the mAbs, CDC is much weaker with ETA due to the structural differences of the respective IgG_1 backbones (ETA does not contain the CH1 domain nor the hinge region)	Jarvis and Faulds, 1999 Moreland *et al.*, 1999 Arend, 2002 Buch *et al.*, 2004 Horiuchi *et al.*, 2010
CER	▪ Human anti-TNF-α mAb Fab region which is conjugated with two cross-linked chains of 20 kDa polyethylene glycol (PEG) ▪ Pegylation extends the plasma half-life of the construct ▪ The construct is unique among the TNFi agents in that it lacks the Fc region of IgG_1	Choy *et al.*, 2002 Horiuchi *et al.*, 2010

Abbreviations: CDC=complement-dependent cytotoxicity; HACAs=human anti-chimeric antibodies; mAb=monoclonal antibody.
1) The mAbs specifically bind to both soluble and membrane-bound human TNF-α with high affinity, forming stable immune complexes; this prevents TNF-α from binding to its membrane-bound receptors.
2) The IgG_1 backbone enables induction of complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC).

Four other types of biological agents, i.e., not targeting TNF, are available as well for the treatment of RA: anakinra (2002), rituximab (1998, approved for RA in 2006), abatacept (2007) and tocilizumab (2009) (Curtis and Singh, 2011). Their mechanisms of action are presented in Table 4.

Table 4. Mechanisms of action of biological agents not targeting TNF.

Drug	Mechanism of action	References
Anakinra	▪ Competitive IL-1 type I receptor antagonist	Cohen *et al.*, 2002
Rituximab	▪ Anti-CD20 mAb that selectively depletes CD20+ B cells, i.e., pre-B cells through mature B cells (but not stem cells or plasma cells)	Cohen *et al.*, 2006
Abatacept	▪ T cell co-stimulation blocker ▪ Structurally a fusion protein consisting of the extracellular domain of human cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and a part of the Fc region of human IgG_1 ▪ By binding to and blocking the CD80/86, it inhibits CD80/86-mediated stimulation of T cells via CD28 located on the surface of the T cell	Ruderman and Pope, 2005
Tocilizumab	▪ Humanized anti-IL-6 receptor alpha (IL-6Rα) mAb ▪ Inhibits the binding of IL-6 to membrane-bound and soluble IL-6Rα, and thereby blocks IL-6 mediated signal transduction ▪ By binding to soluble IL-6Rα, it prevents so called transsignaling by IL-6/IL-6Rα complexes in target cells that lack the ligand-binding IL-6Rα, but contain the ubiquitous signal-transducing IL-6Rβ	Youinou and Jamin, 2009 Ogata and Tanaka, 2012

4.3.2 Treatment options and strategies

The treatment options for RA consist of pharmacological symptom-relieving and/or disease modifying therapies, and non-pharmacological measures, which can include physical, occupational and psychological approaches (Hakala *et al.*, 2009; Smolen *et al.*, 2010a). Pharmacological options include mono- or combination therapy with conventional DMARDs (cDMARDs), biological agents, oral or intra-articular glucocorticoids (GCs), NSAIDs and/or analgesics. Additional therapies may be needed, e.g., to prevent osteoporosis. Non-pharmacological measures include chemosynovectomy or radiosynovectomy (low accessability at present), orthopedic surgery (e.g. arthroplasty), rehabilitation (e.g. physical therapy, occupational therapy), orthoses and aids and patient counseling. Optimal management of RA requires care provided by specialists in rheumatology and a multidisciplinary approach, and shared decision-making with the patient (Hakala *et al.*, 2009; Smolen *et al.*, 2010a; Smolen *et al.*, 2014).

Disease modification constitutes the fundamental therapeutic intervention in RA (Smolen *et al.*, 2010a). During the past couple of decades, DMARD treatment, especially, has undergone significant changes. Firstly, treatment strategies have changed, so that treatment with a cDMARD is started early (as soon as a diagnosis of RA has been made), DMARDs are often used in combinations (combination treatment), appropriate changes to the treatment are made as necessary (the sawtooth principle; Fries, 1990; Box 1), and the principles of tight control (Treat to Target; Smolen *et al.*, 2010b; Box 1) are applied. Secondly, several effective drugs, e.g., biological agents, have become available, and these and older ones have been re-evaluated in order to gain better efficacy, e.g., through combination therapies. New small molecular signal transduction modifying peroral drugs are being developed and tested.

Box 1. The sawtooth strategy and the Treat to Target approach.

Sawtooth
The sawtooth strategy involves serial use of DMARDs to control disease progression, and encompasses the principles of continuous DMARD use started early; setting an individual "disability ceiling"; regular quantitative monitoring of disability; and changing the DMARD treatment when the disability ceiling is reached.

Treat-to-target
The treat-to-target approach involves treatment aiming at remission (low disease activity being an alternative goal in patients with long-standing disease); regular follow-up examinations using composite measures of disease activity (every 1–3 months during active disease); and adjusting the treatment at least every 3 months until the treatment aim is reached.

4.3.3 Treatment aims

The primary aim of the treatment of RA is clinical remission, defined as the absence of signs and symptoms of significant inflammatory disease activity (Hakala *et al.*, 2009; Smolen *et al.*, 2010b). For clinical trials, the ACR and EULAR have recently proposed a provisional definition of remission (Felson *et al.*, 2011a; Felson *et al.*, 2011b). According to this, a patient can be considered to be in remission when swollen joint count (SJC), tender joint count (TJC), CRP (in mg/dl), and the patient global assessment (on a scale of 0 to 10) are all ≤1, or when the score of the Simplified Disease Activity Index (SDAI) is ≤3.3; the SDAI is the simple sum of the SJC (28-joint index), TJC (28-joint index), patient global assessment (0-10 scale), physician global assessment (0-10 scale) and CRP (in mg/dl). However, low disease activity may be the best achievable state and in this respect an acceptable alternative aim, especially in an established, long-standing disease (Smolen *et al.*, 2010b). The treatment target should be maintained throughout the course of the disease, and until it is reached, it is recommended that drug therapy is adjusted every 3-6 months (Smolen *et al.*, 2014). Treatment decisions should be guided by the use of validated composite measures of disease activity, which include joint assessments. In addition, structural changes and functional impairment should be evaluated. Naturally, comorbidities and safety concerns should also be taken into account in all treatment decisions (Smolen *et al.*, 2010a; Smolen *et al.*, 2014). Treatment to target and tight control of RA have been shown to be highly efficacious, and are aimed at symptom control, prevention of structural damage, and normalization of function and social participation (Grigor *et al.*, 2004; Schipper *et al.*, 2010; Smolen *et al.*, 2010b).

4.3.4 Guidelines for the management of RA, with focus on the EULAR recommendations

Many countries, including Finland, have national guidelines for the management of RA, but in this text the EULAR recommendations are described in some detail. The EULAR, ACR and Finnish Current Care recommendations for the use of cDMARDs and bDMARDs in

the management of RA are largely in accordance (Saag *et al.*, 2008; Hakala *et al.*, 2009; Smolen *et al.*, 2010a; Singh *et al.*, 2012; Smolen *et al.*, 2014).

The EULAR recommendations for the management of RA with synthetic (conventional) and biological DMARDs and GCs, based on evidence and expert opinion, state that for the vast majority of patients with RA, the first treatment approach should include a cDMARD, started immediately upon diagnosis (Smolen *et al.*, 2010a; Smolen *et al.*, 2014). A suspected diagnosis of RA may be sufficient for cDMARD treatment initiation. Notably, early RA may be more amenable to disease modification with cDMARDs, showing a greater response rate than is seen in long-standing disease (Anderson *et al.*, 2000). In active RA, MTX is usually the initial DMARD used (alone or as part of cDMARD combination therapy[1]), based on its clinical efficacy (unsurpassed by other cDMARDs) and beneficial long-term safety profile, with its low price being an additional advantage. For patients with contraindications or intolerance to MTX, alternative DMARDs to consider include LEF or SSZ (Smolen *et al.*, 2014). Oral low-dose GC provides additional benefit to DMARD therapy, but should, due to safety concerns in the intermediate to long term, be tapered as soon as clinically feasible.

If the treatment target is not achieved with the first cDMARD strategy, and poor prognosis factors are present, addition of a bDMARD should be considered (Smolen *et al.*, 2014). Poor prognosis factors include the presence of autoantibodies (RF and/or ACPA), especially at high levels; high disease activity, as measured by composite indices, swollen joint counts or acute phase reactants (CRP, ESR); and early occurrence of erosions. In the absence of poor prognostic factors, changing to another cDMARD strategy (including combination therapy) should be considered. If the treatment target is not achieved after switching to another cDMARD, or after combination therapy with cDMARDs, addition of a bDMARD should be considered; indeed, the bDMARD is recommended to be combined with MTX (or other cDMARDs). For patients not achieving the treatment target with a first bDMARD, switching to another bDMARD is recommended. Tofacitinib, a new targeted synthetic DMARD whose mechanism of action is based on janus kinase (JAK) inhibition, may be considered if bDMARD therapy fails; however, tofacitinib is not currently (2013) approved for the treatment of RA in Europe.

Currently, it is unclear how to continue or discontinue treatment in patients who have achieved remission. However, patients are at higher risk of flaring if treatment with cDMARDs is discontinued, and, moreover, remission may be harder to re-achieve upon resumption of treatment (ten Wolde *et al.*, 1997). According to expert opinion, after tapered GC, tapering of bDMARD while continuing concomitant treatment with cDMARD therapy might be considered in cases of persistent remission (e.g. having lasted more than 12 months) (Smolen *et al.*, 2010a; Smolen *et al.*, 2014). Subsequent tapering of cDMARDs is left to the discretion of the patient and doctor.

The FIN-RACo study, pivotal to Finnish rheumatology, compared remission rates and various other outcomes during two years in patients with early RA who received an initial triple therapy (MTX, SSZ and HCQ) and low-dose oral GC, or SSZ monotherapy with or without GC; 63 of 98 patients in this group used GC during the study (Möttönen *et al.*, 1999). Pre-specified treatment adjustments were allowed in both groups, but those in the

[1] cDMARD combination therapies are often specific combinations of two cDMARDs, one of which is usually MTX, or triple therapy with MTX, SSZ and HCQ.

combination arm had to continue SSZ and HCQ until the end of the study. Those in the single-treatment arm were on cDMARD monotherapy (and GC when needed) throughout the study, but could, according to the protocol, replace SSZ with MTX, and subsequently azathioprine; further replacements were allowed using one of prespecified cDMARDs. Of 98 patients, 51 switched to MTX during the study. Remission and ACR50 response rates were higher in the combination arm than in the single-treatment arm throughout the study. The rates tended to improve through the study; at endpoint, the remission rate was 37% in the combination arm and 18% in the single-treatment arm. The corresponding ACR50 response rates were 71% and 58%, respectively. Radiographic outcomes were also better in the combination arm. Notably, at endpoint, oral GC was used by more patients in the single-treatment arm than in the combination arm (50 *vs.* 43). Furthermore, more intra-articular GC injections were given in the single-treatment arm than in the combination arm. Adverse event (AE) frequencies were similar in both groups. After the first two years of the study, the treatment was unrestricted, but still aimed at remission. However, particularly the effectiveness of the initial treatment has been found to be of importance to several long-term outcomes, such as radiological outcomes and work capacity, with results being superior in the initial combination therapy group (Korpela *et al.*, 2004; Puolakka *et al.*, 2004; Rantalaiho *et al.*, 2010).

4.4 Tumor necrosis factor (TNF) and its inhibition in RA

Human TNF-α (hereafter denoted TNF) is a non-glycosylated protein, which in its biologically inactive monomeric form consists of 157 amino acids and has a molecular weight of 17 kDa (Callard and Gearing, 1994; Russo and Polosa, 2005). It is formed from a trans-membrane precursor through proteolytic cleavage by TNF-α converting enzyme (TACE, also known as ADAM17, i.e., a disintegrin and a metallopeptidase 17). Thereafter the soluble monomeric TNF aggregates into biologically active 51 kDa homotrimers. Also trimeric membrane-bound TNF is biologically active. TNF is produced mainly by macrophages, but also e.g. monocytes, T cells, B cells, neutrophils, mast cells and endothelial cells (Hopkins and Meager, 1988; Feldmann and Maini, 2001; Panayi, 2005; Russo and Polosa, 2005; Wright *et al.*, 2011). Almost all potentially noxious stimuli, ranging from physical to chemical and immunological stimuli, have a potential to rapidly induce TNF production and/or release; the activation of macrophages and TNF production in RA has been discussed in the section reviewing the pathogenesis of RA.

4.4.1 TNF and its role in RA pathogenesis

A study by Tetta *et al.* (1990), using a biological assay, revealed TNF at detectable concentrations in the serum of roughly half of RA patients (treated with NSAID ± low-dose GC, but no DMARDs), while not being detected in the serum of healthy control subjects. High concentrations (mean ca 6 ng/ml) were found in the serum of patients with severe RA. TNF was also found in the synovial fluid of about half of the RA patients; the highest synovial fluid TNF concentrations were found in patients with high synovial fluid leukocyte counts (mean TNF concentration ca 5 ng/ml in patients with leukocyte counts of $> 10\times10^9$/l). TNF was not detected in the synovial fluid of osteoarthritis patients. Hopkins and Meager (1988) used an immune-assay and found higher TNF levels in the synovial fluids of patients with seropositive RA than in patients with other arthritides (including

osteoarthritis). In this study, TNF levels did not seem to be associated with synovial fluid cell counts.

The biological responses to TNF are elicited by its binding to TNF receptors, of which two types exist: the 55 kDa Type I receptor (TNFR1, p55 or CD120a), which is constitutively expressed by most cell types and is the main receptor for soluble TNF, and the 75 kDa Type II (TNFR2, p75 or CD120b), the expression of which is highly regulated and which is typically expressed by cells of the immune system, and is the main receptor for membrane-associated TNF (Callard and Gearing, 1994; Varfolomeev and Ashkenazi, 2004; Russo and Polosa, 2005; Parameswaran and Patial, 2010). Deleuran *et al.* (1992), using immunohistochemical staining, found both TNFR types in the rheumatoid synovial membrane and at the cartilage-pannus junction. Since TNFR expressing cells were in the vicinity of TNF producing cells or stained also for TNF, it was reasoned that they are subjected to paracrine and autocrine stimulation. While TNFR expressing cells were also found in osteoarthritic and normal synovial tissue, their numbers were lower and the staining intensity was weaker. Indeed, TNF activates a variety of cell types found in the rheumatoid joint, including macrophages, fibroblast-like synoviocytes, chondrocytes and osteoclasts (Bingham, 2002). Interestingly, also nociceptors have been found to express TNFRs (Schaible, 2010).

The TNFRs trigger several intracellular signaling pathways, and the cellular responses to TNF are remarkably diverse. In the regulation of synovial inflammation, signal transduction through MAP kinase (mitogen-activated protein kinase) and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathways are of central importance (Sweeney and Firestein, 2004; Varfolomeev and Ashkenazi, 2004) (Figure 2). Binding of TNF to TNFR1 leads first to the binding of TRADD, i.e., TNFR-associated death domain protein, to the cytoplasmic phase of the TNFR1. This triggers recruitment of the additional adaptor proteins TNFR-associated factor 2, i.e., TRAF2, and receptor interacting protein-1, i.e., RIP-1 (Devin *et al*., 2000; Sweeney and Firestein, 2004; Russo and Polosa, 2005); TNFR2 recruits TRAF2 directly. The combination of TRAF2 and RIP results in the activation of the IKK (inhibitor of kappa B kinase, i.e., IκB kinase) enzyme complex, which catalyzes phosphorylation and degradation of the NF-κB inhibitor IκB. Subsequently the transcription factor NF-κB is released, whereby it may translocate into the nucleus and activate its target genes, including those of the cytokines TNF, IL-1, IL-2, IL-3, IL-6 and IL-8 (among others); the inflammatory mediators COX-2 and iNOS (inducible nitric oxide synthase); the cell adhesion molecules E-selectin, ICAM-1 (intercellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1); the growth factors G-CSF (granulocyte colony-stimulating factor), M-CSF (macrophage colony-stimulating factor) and GM-CSF (granulocyte macrophage colony-stimulating factor); the cytokine receptor IL-2R; as well as immunoregulatory molecules (including T cell receptors and MHC) and the acute phase protein SAA (serum amyloid A protein) and complement factors (Bingham, 2002; Sweeney and Firestein, 2004). TNF also induces antiapoptotic genes through NF-κB (Varfolomeev and Ashkenazi, 2004). This promotes, e.g., macrophage survival (Lo *et al*., 2011). (However, under other circumstances TNF can activate proapoptotic pathways.)

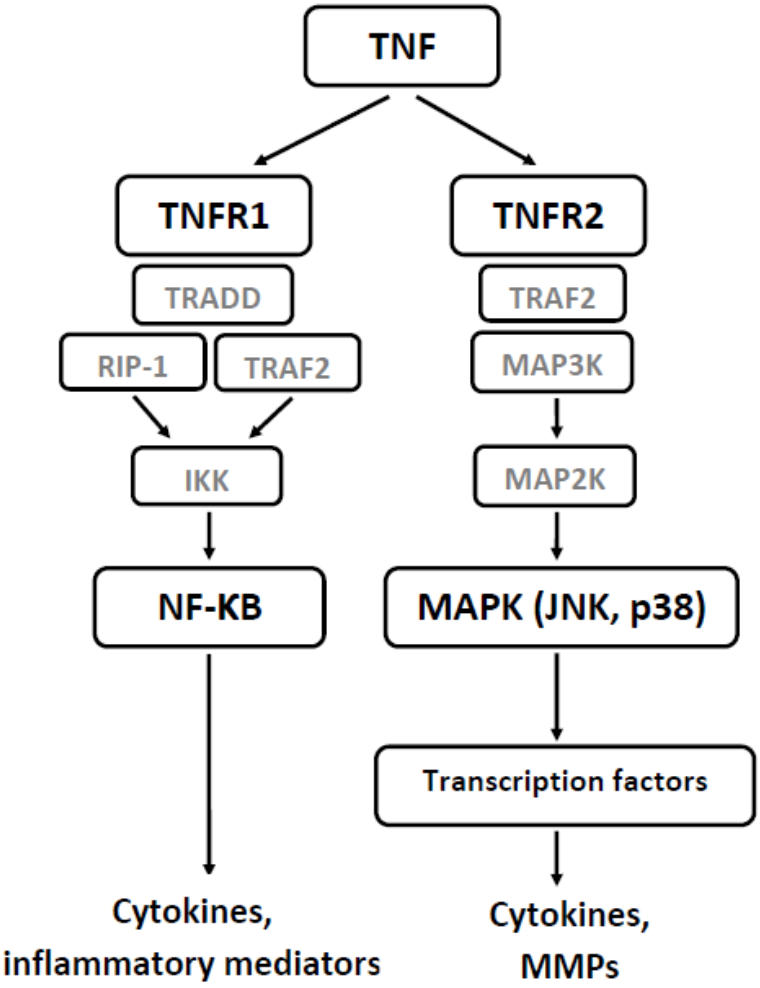

Figure 2. Simplified overview of signal transduction events elicited by TNF (in RA).

Notably, TNF activates NF-κB, and NF-κB targets the TNF gene, whereby a positive feedback loop may be established and results in a persistent inflammation (Wright *et al*., 2011). Moreover, TNF is one of the most prominent elements in the cytokine network regulating synovial inflammation in RA, since it induces the expression of, and has synergistic interactions with, several other proinflammatory cytokines; one such cytokine is IL-1, with which TNF shares many complementary and overlapping activities (Bingham, 2002; Romas *et al*., 2002).

In addition to activating the NF-κB signal transduction pathway, TNF (via TRAF2) also activates the p38 mitogen-activated protein kinases (MAPKs) and c-Jun N-terminal kinases (JNK), which, in turn, activate various transcription factors, such as activator protein 1 (AP-1) from the JNK pathway, leading to increased production of TNF and other cytokines and various metalloproteinases (Kumar *et al.*, 2003; Sweeney and Firestein, 2004; Varfolomeev and Ashkenazi, 2004; Russo and Polosa, 2005). TNF (and certain other cytokines, including IL-1 and IL-6) also stimulates the production of VEGF, the transcription of which is regulated by the transcription factor family known as hypoxia-inducible factor (HIF) (Marrelli *et al*., 2011).

Consequently, TNF is involved in several reciprocally connected pathophysiological phenomena in RA: it triggers local expression of chemokines and cytokines; it promotes adhesion, extravasation, recruitment and activation of inflammatory cells (neutrophils, lymphocytes, monocytes) and the accumulation of synovial fluid; it facilitates the transition from innate to acquired immunity; it stimulates the proliferation of synovial cells; it contributes to the processes of angiogenesis, pannus formation, and cartilage and bone destruction; and it participates in nociception (Bingham, 2002; Nagase and Kashiwagi, 2003; Sweeney and Firestein, 2004; Varfolomeev and Ashkenazi, 2004; Schaible, 2010; Calmon-Hamaty *et al*., 2011).

4.4.2 Clinical effects of anti-TNF agents in RA, with focus on infliximab, etanercept, and adalimumab

Efficacy based on randomized, double-blind, placebo or active-comparator controlled clinical trials

The basis for this section of the literature review is a systematic literature review (SLR) of the efficacy and safety of TNFi agents in the treatment of RA, performed and published by our research group (Aaltonen *et al.*, 2012). To be included in the SLR, patients had to be adults ≥ 16 years of age fulfilling the ACR 1987 revised criteria for the classification of RA, and be randomized either to an intervention or control group. The intervention was required to comprise one of the commercially available biological TNFi agents (IFX, ETA, ADA, CER or GOL), and the control was required to comprise either placebo (PBO) or a combination of PBO and MTX. The TNFi agents had to have the same route of administration as the commercially available products, and be within the same dose range as that recommended for these. Efficacy was to be measured as ACR response rates (ACR20, ACR50 and/or ACR70) at any time point during the study. Additionally, information regarding safety had to be reported. These predefined inclusion criteria were defined so as to encompass the major RCTs performed with TNFi agents in the treatment of RA in an extensive and representative manner.

Most of the resultant RCTs were phase III trials, and most of them were conducted in North America, Europe or Australia. Some eligibility criteria are uniform between the studies. For instance, steady, pre-enrolment doses of oral GC (≤10 mg prednisone equivalent daily dose) and NSAID were allowed, and a washout of DMARDs (other than MTX) was required before commencing the study. However, definitions of active disease varied, and details on these are reviewed for each study separately below. Here, the review of efficacy will focus on ACR response rates, and, where available, remission rates, changes in HAQ score, and radiographic outcomes, although various other efficacy measures may have been reported as well in the individual studies. The focus of the current review will be on IFX, ETA and ADA, as these are the agents included in the experimental section of this thesis; and on efficacy outcomes up to 12 months, in accordance with the published SLR, although some trials have had double-blind or open-label extensions.

Synopsis of the efficacy

The efficacy in terms of ACR20, ACR50 and ACR70 of TNFi agents appears comparable across many trials, and is sometimes summarized as a "60-40-20" rule, i.e., approximately 60%, 40% and 20% of the treated patients reach ACR20, ACR50 and ACR70, respectively (McInnes and O'Dell, 2010). MTX naïve patients with early RA (ERA) consistently show high comparator response rates that are frequently comparable to the rates of TNFi monotherapy after a few weeks or months after commencement; however, a significantly more rapid response is achieved with TNFi therapy (Bathon *et al.*, 2000). A combination therapy with a TNFi agent and concomitant MTX is more effective than TNFi or MTX single therapy in most studies of early or established RA, in terms of both clinical and radiographic outcomes. Some studies indicate that radiographic responses can differ compared to the clinical ACR responses.

Infliximab

The ATTRACT study compared the combination of IFX and MTX (IFX+MTX) with PBO and MTX (PBO+MTX) in patients with active disease despite treatment with MTX (Maini *et al.*, 1999; Lipsky *et al.*, 2000). The ACR response rates at 30 weeks are presented in Table 5; the rates were similar at 54 weeks. In addition, IFX halted the progression of joint damage. The mean change in the radiographic total score at 54 weeks was 1.3 (from a baseline mean value of 79) in the intervention group, compared with 7.0 (from a baseline mean value of 82) in the control group ($p<0.001$; van der Heijde modification of the Sharp scoring system (vdH-S) was used, with a scale of 0 to 440). Interestingly, joint damage was halted in IFX treated patients regardless of their clinical response. IFX had a beneficial effect both on erosions and joint-space narrowing (JSN), and both on hands and feet. Improvements were also seen in physical functioning, as assessed by HAQ, and some other health-related quality of life measures (SF-36 physical component, vitality and social functioning), particularly in the intervention groups with higher and/or more frequent IFX dosage.

Table 5. Summary of ACR response rates in RCTs performed with IFX in the treatment of RA. IFX was used at standard dosage (3 mg/kg intravenously at 0, 2 and 6 weeks, and thereafter every 8 weeks). Bolded values indicate statistically significant differences.

Intervention vs. control; study and/or reference	Inclusion criteria / definition of active disease	ACR20 response rate (%)	ACR50 response rate (%)	ACR70 response rate (%)	Time point of the ACR response evaluation
IFX+MTX vs. PBO+MTX					
ATTRACT; Maini *et al.*, 1999; Lipsky *et al.*, 2000	SJC ≥ 6, TJC ≥ 6, and two of the following: morning stiffness ≥ 45 minutes, ESR > 28 mm/h, and CRP > 2 mg/dl	**50 vs. 20**	**27 vs. 5**	**8 vs. 0**	30 weeks
Abe *et al.*, 2006	Same as in the ATTRACT study	**61 vs. 23**	**31 vs. 9**	**10 vs. 0**	14 weeks
ATTEST; Schiff *et al.*, 2008	SJC ≥ 10, TJC ≥ 12, and CRP ≥ 1 mg/dl	**59 vs. 42**	**37 vs. 20**	**24 vs. 9**	28 weeks
St. Clair *et al.*, 2004	ERA, MTX naïve; SJC ≥ 10, TJC ≥ 12, and at least one of the following: RF positivity, radiographic erosions of the hands or feet, or CRP ≥ 2 mg/dl	**62 vs. 54**	**46 vs. 32**	**33 vs. 21**	54 weeks

ERA=early rheumatoid arthritis

A Japanese RCT of IFX+MTX *vs.* PBO+MTX gave ACR response rates similar to those seen in the ATTRACT study (Abe *et al.*, 2006) (Table 5). The dose of MTX was significantly lower in the Japanese study (with patients of somewhat lower average body weight than that of patients in the U.S. or Europe, and treated according to the Japanese practice which prohibits MTX doses higher than 8 mg/week) than in the ATTRACT study (mean 7.1 mg/week and 7.4 mg/week in the intervention and control group, respectively, *vs.* 16 mg/week).

IFX+MTX and PBO+MTX in the treatment of RA patients with inadequate response to MTX were also compared in the ATTEST trial (Schiff *et al.*, 2008). The ACR response rates at day 197 (approximately 28 weeks) are presented in Table 5. Remission rates (defined as DAS28 score < 2.6) were 13% and 3% for the intervention and control group, respectively.

The ACR response rates of both IFX+MTX and PBO+MTX were comparatively high in MTX naïve patients with active early RA of ≤ 3 years duration (compared to established, long-standing disease) (Clair *et al.*, 2004) (Table 5). Remission rates (defined as DAS28 score < 2.6) were 21% and 15% for the intervention and control group, respectively ($p=0.07$). The mean change in the vdH-S total score was 0.4 (from a baseline mean value of 11.6) in the intervention group, compared with 3.7 (from a baseline mean value of 11.3) in the control group ($p<0.001$). The favorable effect of IFX pertained to both erosion and JSN scores. HAQ scores (scale 0 to 3) improved with a mean ± standard deviation (SD) of 0.80 ± 0.65 in the intervention group, and 0.68 ± 0.63 in the control group ($p<0.05$).

A magnetic resonance imaging (MRI) study, involving a small number of patients with RA symptom duration < 12 months, rendered significantly higher ACR response rates at 14 and 54 weeks in the IFX+MTX group, compared with the PBO+MTX group (Quinn *et al.*, 2005). IFX+MTX treatment led to a significant reduction in the MRI detected synovitis and, at 54 weeks, there were no new erosions in this group.

Etanercept

ETA monotherapy vs. PBO

Moreland *et al.* (1999) compared ETA 25 mg subcutaneously (s.c.) twice weekly (standard dosage) as monotherapy (i.e., no concomitant DMARDs were permitted during the study), with PBO, in RA patients with active disease, who had discontinued one to four DMARDs due to lack of effect. The ACR response rates at three months are presented in Table 6; the rates were similar at six months. HRQOL, as measured by HAQ, also improved significantly in the intervention group. Treatment benefits were uniform irrespective of NSAID or GC usage or body weight. In a study by Keystone *et al.* (2004a), ETA monotherapy at 25 mg twice weekly or 50 mg once weekly rendered ACR20 response rates at 8 weeks of 47% and 51%, respectively, compared to 21% for PBO.

Table 6. Summary of ACR response rates in RCTs performed with ETA in the treatment of RA. ETA was used at standard dosage (25 mg subcutaneously twice weekly, or 50 mg once weekly). Bolded values indicate statistically significant differences.

Intervention vs. control; study and/or reference	Inclusion criteria / definition of active disease	ACR20 response rate (%)	ACR50 response rate (%)	ACR70 response rate (%)	Time point of the ACR response evaluation
ETA (mono) vs. PBO					
Moreland *et al.*, 1999	SJC ≥ 10, TJC ≥ 12 and at least one of the following: morning stiffness ≥ 45 minutes, ESR ≥ 28 mm/h, and CRP > 2 mg/dl	**62 vs. 23**	**41 vs. 8**	**15 vs. 4**	12 weeks
ETA (mono) vs. MTX					
TEMPO; Klareskog *et al.*, 2004	SJC ≥ 10, painful joint count (PJC) ≥ 12, and at least one of the following: morning stiffness ≥ 45 minutes, ESR ≥ 28 mm/h, and CRP ≥ 2 mg/dl	76 vs. 75	48 vs. 43	24 vs. 19	52 weeks
Bathon *et al.*, 2000	ERA, MTX naïve; SJC ≥ 10, TJC or PJC ≥ 12, and at least one of the following: morning stiffness ≥ 45 minutes, ESR ≥ 28 mm/h, and CRP ≥ 2 mg/dl; RF positive or at least 3 radiographic bone erosions in the hands, wrists or feet.	72 vs. 65			52 weeks
ETA+MTX vs. PBO+MTX					
Weinblatt *et al.*, 1999	SJC ≥ 6 and TJC ≥ 6	**66 vs. 33**	**42 vs. 0**	**15 vs. 0**	12 weeks
TEMPO; Klareskog *et al.*, 2004	See earlier	**85 vs. 75**	**69 vs. 43**	**43 vs. 19**	52 weeks
COMET; Emery *et al.*, 2008	ERA, MTX naïve; DAS28 ≥ 3.2, and ESR ≥ 28 mm/h or CRP ≥ 2 mg/dl	**86 vs. 67**	**71 vs. 49**	**48 vs. 28**	52 weeks

ETA monotherapy vs. MTX

ETA 25 mg s.c. twice a week monotherapy was compared with MTX in the treatment of active RA in the TEMPO trial (Klareskog *et al.*, 2004). Eligible patients had to have an insufficient response, at the discretion of the investigator, to at least one DMARD other than MTX. ACR response rates at 52 weeks were similar for ETA monotherapy and MTX (Table 6). Remission rates (defined as DAS < 1.6) were also similar in the ETA monotherapy and MTX groups (16% and 13%, respectively), as were also the mean HAQ improvements (1.7 to 1.0 and 1.7 to 1.1, respectively). However, radiographic outcomes were superior in the ETA monotherapy group. In this group, the mean change in the total Sharp score was 0.52 (from 21.8 at baseline), compared with 2.80 (from 26.8 at baseline) in the MTX group ($p<0.05$). The mean change in erosion score was 0.21 and 1.68, respectively ($p<0.01$), and the mean change in JSN score was 0.32 and 1.12 (not statistically significantly different). The proportion of patients without radiographic progression (change in total score ≤ 0.5) was 68% and 57%, respectively ($p<0.05$).

A study by Bathon *et al.* (2000) compared ETA (25 mg s.c. twice a week) monotherapy with MTX in MTX naïve patients with active early RA of ≤ 3 years duration. ACR response rates were significantly higher ($p<0.05$) in the ETA monotherapy group than in the MTX group at most evaluations during the first six months, but were approximately the same thereafter (up to 12 months) (Table 6). Also radiographic assessments indicated that ETA monotherapy had a more rapid effect. At six months, the mean total Sharp score had increased by 0.57 (from a mean of 2.4 at baseline) in the ETA monotherapy group, compared with 1.06 (from a mean of 12.9 at baseline) in the MTX group ($p=0.001$); at 12 months the corresponding increases were 1.00 and 1.59 ($p=0.11$). At the end of the study, the erosion score had not increased in 72% of the patients receiving ETA monotherapy, compared with 60% of those receiving MTX ($p<0.01$). The mean increase in the modified Sharp erosion score was 0.30 and 0.68 ($p=0.001$) at six months for the two groups, respectively; at 12 months the corresponding figures were 0.47 and 1.03, respectively ($p=0.002$). No significant differences between the treatment groups were found for the changes in JSN. In this study, the patients with the best clinical improvement (especially in CRP) had the least evidence of radiographic progression.

Combination of ETA and MTX

ETA+MTX and PBO+MTX were compared in RA patients with active disease despite treatment with MTX (Weinblatt *et al.*, 1999). ACR response rates at 12 weeks were similar to those seen in the study by Moreland *et al.* (1999) (Table 6), with similar responses at 24 weeks. The median HAQ score improved from 1.5 at baseline to 0.8 at 24 weeks in the intervention group, while it did not change significantly in the control group. The efficacy of ETA+MTX was superior to that of the PBO+MTX regardless of NSAID or GC usage or the MTX dose. Compared to this study, a Taiwanese RCT rendered similar or somewhat higher ACR response rates at 12 weeks: in the ETA+MTX group the ACR20, ACR50 and ACR70 response rates were 90%, 66% and 24%, respectively, and in the PBO+MTX group 34%, 10% and 0%, respectively (Lan *et al.*, 2004).

The TEMPO trial compared ETA+MTX with ETA and MTX as single therapies (Klareskog *et al.*, 2004). Efficacy outcomes of the single therapies are reviewed above; here, the outcomes of the combination treatment are reviewed. ACR response rates at 52 weeks were superior in the combination therapy group compared to the single therapies (Table 6). The remission rate was 35% ($p<0.0001$ for the combination therapy *vs.* single therapies), and the mean HAQ score improved from 1.8 to 0.8 ($p<0.0001$ for the combination therapy *vs.* single therapies). Mean negative radiographic progression scores were seen in the combination group, indicating repair of joint damage. The mean change in the total Sharp score, the erosion score and the JSN score were -0.54 ($p<0.001$ for the combination therapy *vs.* single therapies), -0.30 ($p<0.0001$ for the combination therapy *vs.* MTX), and -0.23 ($p<0.001$ or less for the combination therapy *vs.* single therapies). The proportion of patients without radiographic progression was 80% ($p<0.005$ or less for the combination therapy *vs.* single therapies).

In the study by Keystone *et al.* (2004a), ETA 25 mg twice weekly, ETA 50 mg once weekly, or PBO with or without concomitant MTX rendered ACR20 response rates at 8 weeks (the primary efficacy end point) of 51%, 49% and 17%, respectively. In this study, MTX usage did not have a significant impact on the achievement of the response. Additionally, sex, race, body weight, age, and individual ACR core set measures at baseline did not significantly affect the achievement of the primary efficacy end point.

The COMET trial compared the combination of ETA 50 mg once weekly and MTX to PBO+MTX in the treatment of MTX naïve patients with active early RA of ≤ 2 years duration (Emery *et al.*, 2008). ACR response rates at 52 weeks of both combination and control treatments were similar or somewhat higher compared to those seen in other trials performed on patients long-standing disease (Table 6). Remission (defined as DAS28 < 2.6) was achieved by 50% and 28% of the respective groups ($p<0.0001$). The HAQ score improved from 1.7 to 0.7 in the combination group, and from 1.6 to 0.9 in the MTX group ($p<0.0001$). Radiographic non-progression (change in vdH-S total score ≤ 0.5) was seen in 80% and 59% of the respective groups ($p<0.0001$). The change in the radiographic total score, from baseline to 52 weeks, was 0.27 and 2.44 in the two groups, respectively; the change in the total score seemed to be driven by joint erosion, rather than by JSN. Fewer patients in the combination group stopped working during the study (9% *vs.* 24%, $p<0.005$).

Adalimumab

ADA monotherapy vs. PBO

van de Putte *et al.* (2003) compared ADA (20 mg s.c. once weekly, phase II study) monotherapy with PBO in the treatment of patients for whom treatment with at least one DMARD had failed. The ACR response rates at 12 weeks are presented in Table 7. HAQ improved from 1.8 to 1.3 in the intervention group, but stayed at 1.6 in the control group ($p\leq 0.001$). Similar results were seen in a phase III study, where ADA was used at a standard dosage (40 mg every other week) (van de Putte *et al.*, 2004; Table 7). Concomitant GC treatment did not seem to affect the response (ACR20, the primary efficacy end point) to ADA.

Table 7. Summary of ACR response rates in RCTs performed with ADA in the treatment of RA. ADA was used at standard dosage (40 mg subcutaneously every other week), except in van de Putte *et al.* (2003) where the dosage was 20 mg once weekly. Bolded values indicate statistically significant differences.

Intervention vs. control; study and/or reference	Inclusion criteria / definition of active disease	ACR20 response rate (%)	ACR50 response rate (%)	ACR70 response rate (%)	Time point of the ACR response evaluation
ADA (mono) vs. PBO					
van de Putte *et al.*, 2003	SJC ≥ 10 and TJC ≥ 12, and either ESR ≥ 28 mm/h or CRP ≥ 2 mg/dl	**51 vs. 10**	**24 vs. 1**	**11 vs. 0**	12 weeks
van de Putte *et al.*, 2004	Same as van de Putte *et al.*, 2003	**46 vs. 19**	**22 vs. 8**	**12 vs. 2**	26 weeks
CHANGE; Miyasaka, 2008	SJC ≥ 10 and TJC ≥ 12, and CRP ≥ 2 mg/dl	**43 vs. 13**	**21 vs. 3**	**17 vs. 1**	12 weeks
ADA (mono) vs. MTX					
PREMIER; Breedveld *et al.*, 2006	SJC ≥ 8, TJC ≥ 10, and either ESR ≥ 28 mm/h or CRP ≥ 1.5 mg/dl; RF positive or at least one joint erosion.	**54 vs. 63**	41 vs. 46	26 vs. 28	52 weeks
ADA+MTX vs. PBO+MTX					
ARMADA; Weinblatt *et al.*, 2003	SJC ≥ 6 and TJC ≥ 9	**67 vs. 15**	**55 vs. 8**	**27 vs. 5**	24 weeks
Keystone *et al.*, 2004b	SJC ≥ 6, TJC ≥ 9 and CRP > 1 mg/dl; RF positive or at least one radiographic joint erosion in the hands or feet.	**63 vs. 30**	**39 vs. 10**	**21 vs. 3**	24 weeks
Chen *et al.*, 2009	SJC > 6 and TJC > 9 for at least 3 months	54 vs. 33	34 vs. 17	14 vs. 0	12 weeks
PREMIER; Breedveld *et al.*, 2006	See earlier	**73 vs. 63**	**62 vs. 46**	**46 vs. 28**	52 weeks

The Japanese CHANGE trial used a similar study design as that of van de Putte *et al.* to compare ADA monotherapy (20 mg, 40 mg or 80 mg every other week) with PBO (Miyasaka, 2008). The ACR response rates at 12 weeks are presented in Table 7. The rates were similar at 24 weeks, despite a larger proportion of patients having developed anti-ADA antibodies (Abs) (44% in the CHANGE trial *vs.* 12% in the study by van de Putte *et al.*, 2004). Anti-ADA Ab concentrations were relatively low in most cases though. The ACR20 response rate at 24 weeks (the primary efficacy end point) was lower among the anti-ADA Ab positive patients than among the anti-ADA Ab negative patients (28% *vs.* 57%). This was in contrast to the study by van de Putte *et al.* (2004), where the ACR20 response rate after 26 weeks of ADA monotherapy at standard dosage did not differ significantly between the anti-ADA Ab positive and negative patients.

ADA monotherapy vs. MTX

Breedveld *et al.* (2006) compared single therapies of ADA (the standard dosage 40 mg s.c. every other week) or MTX in the treatment MTX naïve patients with active early RA of < 3 years duration in the PREMIER study. ACR response rates at one year in patients treated with ADA monotherapy were not superior to those seen in the MTX group (Table 7). Remission (defined as DAS28 < 2.6) was achieved by 23% and 21% of the respective groups. The mean HAQ score improved from 1.6 to 0.8 in the ADA group, and from 1.5 to 0.7 in the MTX group. The ACR response and remission rates and the HAQ improvements were similar after two years. Interestingly, despite the comparable clinical efficacy of ADA and MTX monotherapies, there was significantly less radiographic progression in the ADA group. In this group, the mean change in the modified total Sharp score was 3.0 at one year and 5.5 at two years (from 18.8 at the baseline), compared with 5.7 at one year and 10.4 at two years in the MTX group (from 21.9 at the baseline) ($p<0.001$). In the ADA group, the mean change in the erosion score was 1.7 at one year and 3.0 at two years, compared with 3.7 at one year and 6.4 at two years in the MTX group. The mean changes in the JSN score at one and two years were 1.3 and 2.6, respectively, in the ADA group, and 2.0 and 4.0, respectively, in the MTX group. A larger proportion of patients in the ADA group had no radiographic progression (change in the total score ≤ 0.5), compared with the MTX group (at one year, 51% and 37% for the two groups, respectively, and at two years, 45% and 34%, respectively; $p<0.01$).

Combination of ADA and MTX

The ARMADA trial compared ADA 40 mg s.c. every other week (standard dosage) and concomitant MTX with PBO+MTX in the treatment of patients with active RA despite treatment with MTX (Weinblatt *et al.*, 2003). The ACR response rates at 24 weeks are presented in Table 7. A Korean study (Kim *et al.*, 2007) rendered ACR response rates of a similar range as those seen in the ARMADA trial, although with a comparatively higher ACR20 rate in the control group; at 24 weeks, the ACR20, ACR50 and ACR70 response rates in the intervention group were 62%, 43% and 22%, respectively, and in the control group, 37%, 14% and 8%, respectively.

Also a study by Keystone *et al.* (2004b) assessed outcomes of ADA at a standard dosage with concomitant MTX (dosage similar to that used in the ARMADA trial), and compared them with PBO+MTX in patients with active RA despite treatment with MTX. The ACR response rates at 24 weeks are presented in Table 7. HAQ improved from 1.5 to 0.9 in the intervention group, compared to a change from 1.5 to 1.2 in the control group ($p\leq0.001$). The ACR response rates and HAQ improvements were similar at 52 weeks. Compared with PBO, treatment with ADA also led to significantly better outcomes in all SF-36 domains, except the emotional role domain. Radiographic outcomes were also superior in the intervention group. At the 52 week assessment, the mean change in the modified total Sharp score was 0.1 and 2.7 for the two groups, respectively ($p\leq0.001$). The mean change in erosion score was 0.0 and 1.6, respectively ($p\leq0.001$). No new erosions were seen in 62% and 46%, respectively ($p\leq0.01$), and improved erosion scores were seen in 38% and 19%, respectively ($p\leq0.001$). The mean change in JSN score was 0.1 and 1.0, respectively ($p\leq0.01$).

Chen *et al.* (2009) compared the efficacy of treatment with ADA+MTX to that of treatment with PBO+MTX in Taiwanese patients with an active RA. The ACR response rates at 12 weeks are presented in Table 7. Despite the trend for higher response rates in the combination group, they were not statistically significantly better than the corresponding rates in the MTX group, perhaps due to the relatively small number of patients in the groups (35 and 12, respectively). However, a statistically significant difference in HAQ improvement was found; the HAQ score improved from 1.7 at the baseline to 1.1 at 12 weeks in the combination arm, compared with a change from 1.8 to 1.6 in the control arm ($p<0.05$).

The PREMIER trial compared ADA+MTX with ADA and MTX as single therapies in the treatment of early RA (Breedveld *et al.*, 2006). Efficacy outcomes of the single therapies are reviewed above; here, the outcomes of the combination treatment are reviewed. The ACR response rates at one year are presented in Table 7; the rates were similar at two years. Remission was achieved by 43% and 49% at one and two years, respectively. The mean HAQ score improved from 1.5 at the baseline to 0.4 at one year, with a similar improvement at two years. The ACR response and remission rates and HAQ improvements were better in the combination arm than in the single treatment arms ($p<0.05$ or less), except for the HAQ score of the ADA+MTX combination *vs.* ADA monotherapy at two years ($p=0.06$). The radiographic outcomes were better in the combination arm than in the single treatment arms. At one and two years, the total Sharp score increased by a mean of 1.3 and 1.9 (from 18.1 at the baseline), the erosion score by a mean of 0.8 and 1.0, respectively, and the JSN score by a mean of 0.5 and 0.9, respectively ($p<0.005$ compared with the single therapies). The proportion of ADA+MTX treated patients with no radiographic progression was 64% at one year and 61% at two years ($p<0.01$ compared with the single therapies).

Safety based on systematic literature review and meta-analysis of RCTs

The safety assessments in our SLR and meta-analysis were based on the same RCTs that were selected for the efficacy assessments, and focused on discontinuations due to AEs and occurrences of any AE, serious adverse events (SAEs), any infection, serious infections and infusion or injection-site reactions (Aaltonen *et al.*, 2012). These will be the focus in the present RCT review as well. The assessments include all dosages studied in the trials. However, higher doses of IFX or ADA were not associated with higher rates of AEs or discontinuation due to AEs. In contrast, infusion reactions were less likely to occur in patients on high doses of IFX, compared to those on standard dosage (RR 0.7, $p<0.05$). Effects of higher than standard doses of ETA were not studied in the RCTs included in the SLR.

Infliximab

IFX+MTX treated patients had a 2-fold risk of treatment discontinuation due to an AE, compared to those treated with PBO+MTX ($p<0.05$) (Aaltonen *et al.*, 2012). The occurrences of AEs, SAEs, infections, and serious infections were comparable between the two groups. However, the risk of infusion reaction was somewhat increased in the intervention group (risk ratio (RR) 1.8; $p<0.05$).

Etanercept

Intervention was not associated with a higher discontinuation rate due to AE in any of the comparisons, i.e., ETA *vs.* PBO, ETA *vs.* MTX, ETA+MTX *vs.* MTX, and ETA+MTX *vs.* ETA (Aaltonen *et al.*, 2012). In fact, RRs for the interventions were < 1, indicating a lower risk of discontinuation due to AE. However, only the pooled analysis (ETA *vs.* any control) showed a statistically significant result, with a RR of 0.7 ($p<0.05$). The interventions were not associated with higher rates of AEs, SAEs, infections, and serious infections (ETA *vs.* PBO was not numerically assessable). However, ETA with or without concomitant MTX was associated with a higher risk of injection-site reactions, compared to the control arms that did not include ETA (ETA *vs.* PBO, RR 3.9; ETA *vs.* MTX, RR 6.9; ETA+MTX *vs.* MTX, RR 4.4; all $p<0.05$); the RR for ETA+MTX *vs.* ETA was 0.5 ($p<0.05$). The pooled estimate was 4.5 ($p<0.05$).

Adalimumab

Treatment with ADA+MTX was associated with a higher discontinuation rate due to AE than the treatment with PBO+MTX (RR 1.6, $p<0.05$) (Aaltonen *et al.*, 2012). The relative risks were not statistically significantly higher in the other comparisons, i.e., ADA *vs.* PBO, ADA *vs.* MTX, and ADA+MTX *vs.* ADA; the pooled RR was 1.6 ($p<0.05$). Intervention was not associated with higher rates of AEs overall. Moreover, intervention was not associated with higher rates of SAEs or infections in the two numerically assessable comparisons, i.e., ADA *vs.* PBO and ADA+MTX *vs.* MTX. Although the relative risks for serious infections seemed higher for most of the interventions, they were not statistically significantly different from the control treatments (ADA *vs.* PBO, RR 4.2; ADA+MTX *vs.* MTX RR 2.4; ADA+MTX *vs.* ADA, RR 3.1); the RR for ADA *vs.* MTX was 0.4. ADA was associated with a higher rate of injection-site reactions compared to PBO (RR 7.7, $p<0.05$). However, ADA+MTX was not associated with a higher risk compared with PBO+MTX. The pooled estimate was 3.1 (not statistically significant).

Comparison to other RCT-based systematic literature reviews and meta-analyses of safety

To confirm the results of the RCT-based SLR and meta-analysis of safety data performed by Aaltonen *et al.*, (2012), comparisons were made to earlier published data on the same topic where similar methodology was used (Table 8).

Table 8. Comparison of RCT-based SLR and meta-analysis of safety. Where not otherwise specified, the TNFi agents were used at standard dosages. Risk ratios and odds ratios refer to intervention *vs.* control, unless otherwise stated.

Reference	Bongartz *et al.*, 2006	Alonso-Ruiz *et al.*, 2008	Leombruno *et al.*, 2009	Result compared to Aaltonen *et al.*, 2012
Trial durations Number of RCTs	3-12 months IFX, 4 ADA, 5 ETA, 0	6-24 months IFX, 4 ADA, 5 ETA, 4	2-24 months IFX, 5 ADA, 6 ETA, 7	3-12 months IFX, 5 ADA, 8 ETA, 7
Treatment discontinuation due to AE	n.a.	IFX, RR 2.0; p<0.05 ADA, RR 1.4; p<0.05 ETA, RR 0.7; p<0.05 Pooled, p=ns	n.a.	Similar
AE rate	n.a.	IFX, p=ns ADA, p=ns ETA, p=ns Pooled, RR 1.02; p<0.05	n.a.	Similar
SAE	n.a.	IFX, RR 1.4; p<0.05 ADA, p=ns ETA, p=ns Pooled, p=ns	IFX, p=ns ADA, p=ns ETA, p=ns	IFX was not associated with a higher SAE rate
Infection	n.a.	IFX, RR 1.2; p<0.005 ADA, p=ns ETA, p=ns Pooled, p=ns	n.a.	IFX was not associated with a higher infection rate
Serious infection	Low-dose IFX or ADA[2], OR 1.8; p<0.05 High-dose IFX or ADA[3], OR 2.3; p<0.05 Overall, OR 2.0; p<0.05	IFX, p=ns ADA, p=ns ETA, p=ns Pooled, p=ns High-dose IFX[1], p<0.01	IFX, p=ns ADA, p=ns ETA, p=ns High-dose IFX or ADA[5], RR 1.8; p<0.05	Differences between intervention and control were not statistically significant. High dose IFX vs. standard dose, RR 1.5, p=ns
Infusion reaction	n.a.	IFX, RR 2.7; p<0.05	n.a.	Similar
Injection-site reaction	n.a.	ADA, RR 1.7; p<0.05 ETA, RR 5.1; p<0.05	n.a.	Similar. However, the pooled estimate for ADA (RR 3.1) was not statistically significant.
Malignancy[4]	Low-dose IFX or ADA[2], OR 1.4; p=ns High-dose IFX or ADA[3], OR 4.3; p<0.05 Overall, OR 3.3; p<0.05	IFX, p=ns ADA, p=ns ETA, p=ns Pooled, p=ns High-dose IFX[1], p=ns	IFX, p=ns ADA, p=ns ETA, p=ns	n.a.
Mortality	n.a.	IFX, p=ns ADA, p=ns ETA, p=ns Pooled, p=ns	IFX, p=ns ADA, p=ns ETA, p=ns	n.a.

n.a., not assessed in the study; ns, not significant.

1) IFX dose up to 10 mg/kg every 4 weeks; assessments of high-dose ADA and ETA were not possible to perform.
2) Low dose defined as IFX ≤ 3 mg/kg every 4 weeks or ADA 20 mg weekly
3) High dose defined as IFX ≥ 6 mg/kg every 8 weeks or ADA 40 mg every other week
4) Malignancies assessed in Leombruno *et al*. (2009) were lymphomas, non-melanoma skin cancers, and the composite endpoint of non-cutaneous cancer or melanoma
5) IFX doses were up to 10 mg/kg every 4 weeks and ADA doses up to 80 mg weekly; on average, high doses were 2 to 3 times higher than the standard doses. No RCTs evaluated high doses of ETA.

The results regarding treatment discontinuations due to AE, AE rates, and infusion or injection-site reactions were largely similar when comparing earlier studies with that of Aaltonen *et al.*, (2012). The main discrepancies among the studies relate to the occurrence of SAEs and infections in IFX treated patients, and the occurrence of serious infections in anti-TNF mAb treated patients. In the study by Leombruno *et al.* (2009), the risk of serious infection (all dosages of all three TNFi agents analyzed) decreased significantly with an increasing trial duration ($p<0.05$). Other dose- or time-dependencies were not found in their study (i.e., when assessing risk of death, SAEs and malignancies).

Safety based on observational studies, with focus on infections and cancer

Observational data indicates that mortality due to cardiovascular disease (CVD), infection or cancer is lower in TNFi treated patients, compared with RA patients not treated with these agents (Dixon *et al.*, 2006; Carmona *et al.*, 2007; Galloway *et al.*, 2011). One study found an association between TNFi therapy and a reduced mortality in women, but not in men, with RA (Jacobsson *et al.*, 2007).

Observational data regarding the risk of infections in TNFi treated RA patients (*vs.* cDMARD treated patients) have yielded mixed results. Dixon *et al.* (2006) did not find evidence of an increased overall risk of serious infections, after adjustment for the baseline risk (age, sex, disease severity, comorbidity, extra-articular manifestations, GC use, and smoking). However, the rate of serious skin and soft tissue infections was increased in the TNFi treated patients (ca 4-fold). In addition, serious intracellular bacterial infections occurred exclusively in the TNFi treated cohort (19 of 7,664 *vs.* 0 of 1,354). Galloway *et al.* (2011) observed a small but significant overall risk of serious infection in TNFi treated patients (hazard ratio (HR) 1.2, adjusted for age, sex, disease activity, disease duration, smoking, GC use, and comorbidities). Notably, the risk of infections was highest during the first six months of therapy (HR 1.8). Wolfe *et al.* (2006) observed a dose-related association between GC use and hospitalization due to pneumonia, but no increased risk due to TNFi therapy. In a study by Listing *et al.* (2005), the RR for infections overall was 4.1 for IFX and 3.3 for ETA; the RR of serious infection was 2.7 and 2.8, respectively. RRs adjusted for age, number of DMARD failures, DAS28, CRP level, RF positivity, and disability were 3.0 and 2.3, respectively, for infections overall, and 2.1 and 2.2, respectively, for serious infections. The adjusted RRs for serious infections were not statistically significant. Among the infections found more frequently in TNFi treated patients were serious and non-serious respiratory tract infections, bacterial skin and subcutaneous tissue infections, and bone and joint infections. In a series of 60 consecutive IFX or ETA treated patients, prospectively followed up for up to 33 months at a Swiss university hospital department of rheumatology, 11 contracted a serious infection (Kroesen *et al.*, 2003). The incidence of serious infections was 0.181 per year of TNFi treatment, *vs.* 0.008 in the two preceding years.

The risk of solid cancer does not appear to be increased among TNFi treated RA patients during the first five years of therapy (Askling *et al.*, 2005; Setoguchi *et al.*, 2006; Furst *et al.*, 2012). Results concerning risk of hematologic (lymphoproliferative) malignancies remain inconclusive (Setoguchi *et al.*, 2006). Some studies have found an increased risk among RA patients treated with TNFi agents, with an up to 5-fold hazard rate for lymphoma (Wolfe and Michaud, 2004; Geborek *et al.*, 2005; Setoguchi *et al.*, 2006). However, the possibility of selection bias could not be excluded.

Scientific evidence gives reason to consider infections and malignancies as possible adverse effects of TNFi therapy. The effects of TNF and, by extension, TNFi therapy, on cancer are complex (Balkwill, 2006). Paradoxically, TNF seems to have tumor suppressing and tumor promoting effects, depending on the context; many of them are yet to be further elucidated (Balkwill, 2002). TNF may act to suppress tumors by acting as an important effector molecule in $CD8^+$ T-cell and natural killer (NK)-cell mediated killing of immunogenic tumor cells. In addition, high doses of therapeutically administered TNF can induce apoptosis and necrosis of tumor cells and destroy tumor vasculature. However, chronic production of TNF in the tumor microenvironment may enhance tumor development and spread via mechanisms often shared with inflammatory processes. For example, TNF can contribute to tissue remodeling and stromal development necessary for tumor growth and spread; induce other effector molecules, such as chemokines, cytokines, angiogenic factors, MMPs, and adhesion molecules; contribute to DNA damage via oxidative stress; and enhance the growth and survival of tumor cells.

TNF is involved in the host defense against infectious agents in that it induces chemokines, cytokines, and endothelial adhesion molecules and leads to proliferation, activation, and directed migration of leukocytes (Ehlers, 2003; Furst *et al.*, 2006). In addition, TNF is vital to the formation and maintenance of granulomas, i.e., cell collections consisting of macrophages, T cells and various other host cells (Ehlers, 2003; Tufariello *et al.*, 2003; Furst *et al.*, 2006). Granulomas are formed when acute inflammatory processes are unable to destroy an invading agent, such as *Mycobacterium tuberculosis*, which then resides within the macrophages. The granuloma functions as an immune microenvironment to facilitate interactions between the cells contained therein, a continuous and dynamic process. The granuloma essentially contains the infectious agent in a latent form, confining it to the granulomas.

Neutralization of TNF can interfere with these host defense mechanisms and increase the susceptibility to infections. Furthermore, TNFi therapy may inhibit phagosome maturation in macrophages and increase regulatory T cell (T_{reg}) function, which may increase the susceptibility to tuberculosis (TB) (Harris *et al.*, 2008; Harris and Keane, 2010). Early on (during phase III RCTs and early post-marketing surveillance), it became apparent that TNFi therapy indeed increases the risk of TB and other granulomatous infections (Wallis *et al.*, 2004). This has mandated TB screening and treatment of individuals at risk of developing TB due to, e.g., a latent infection or with an active infection, prior to starting TNFi therapy (Tufariello *et al.*, 2003; Singh *et al.*, 2012).

Although these precautionary measures have significantly decreased the risk, a continuous vigilance is needed as the risk is not completely eliminated (e.g., due to anergy and false-negative skin test result), as activation of latent TB may be difficult to identify in patients treated with systemic GCs and TNFi, as the presentation of TB associated with TNFi therapy is frequently atypical (extrapulmonary or disseminated TB), and as screening tests are not routinely available for other latent granulomatous infections (Tufariello *et al.*, 2003; Furst *et al.*, 2006; Gómez-Reino *et al.*, 2007). Interestingly, the incidence of TB and other granulomatous infections appears to be higher in IFX than ETA treated patients (Wallis *et al.*, 2004; Furst *et al.*, 2006). This may be due to differences between the TNF binding avidity of the agents, their pharmacokinetics (e.g., half-life, peak concentration), antibody-mediated cell lysis (which, e.g., can lead to monocytopenia), their ability to induce apoptosis of monocytes and T cells, or to inhibit IFN-γ production. Ehlers (2003) points out

that a complete neutralization of TNF must be avoided; TNFi therapy of RA should inhibit TNF activity significantly to reduce the disease activity, but still only partially to allow sufficient TNF activity to resist infections.

Other clinical effects and special considerations

Autoimmunity and immunogenicity

In RCTs, the proportion of patients who have newly become positive for anti-nuclear Abs (ANA) has ranged from 11% to 12% in ADA treated patients, and up to 40% in IFX treated patients; the percentages in the control groups have ranged from 6% to 11% (Weinblatt *et al.*, 2003; Keystone *et al.*, 2004b; St. Clair *et al.*, 2004; van de Putte *et al.*, 2004). Antibodies (Abs) to double-stranded DNA (dsDNA) have been reported usually in <10% of IFX, ADA or ETA treated patients; in one study on IFX, the percentage was 24% (Maini *et al.*, 1999; Moreland *et al.*, 1999; Weinblatt *et al.*, 1999; Weinblatt *et al.*, 2003; Keystone *et al.*, 2004b; St. Clair *et al.*, 2004). The percentages in the control groups have ranged from 0% to 3%. However, lupus-like reactions or other connective tissue disorders developed infrequently during the TNFi trials.

The reported frequencies of anti-drug Abs (ADAbs) against the anti-TNF mAbs (IFX and ADA) vary between the studies where this has been assessed. Up to nearly half of IFX treated patients may develop such Abs during the first year of therapy (Haraoui *et al.*, 2004; Abe *et al.*, 2006; Wolbink *et al.*, 2006). Development of anti-ADA Abs has been reported in 12% during six months in one study, and 44% in another (van de Putte *et al.*, 2004; Miyasaka *et al.*, 2008). ADAbs may be associated with lower response rates and somewhat higher frequencies of infusion reactions or injection-site reactions. No other clinically important differences between AEs were apparent in the RCTs. Anti-ETA Abs develop in ≤3% of patients, and they have been non-neutralizing Abs (Bathon *et al.*, 2000; Keystone *et al.*, 2004a).

Cardiovascular effects

So far, clinical trials of TNFi agents (and other bDMARDs) have not principally focused on nonarticular manifestations of RA. However, the role of TNF and the effects of TNFi therapy on CVDs has been a matter of considerable interest owing to the predisposition of RA patients to morbidity and premature or accelerated mortality due to CVD, and recognition of the involvement of inflammatory processes and TNF in atherosclerosis and heart failure (Mikuls, 2003; Anker and von Haehling, 2004; Sihvonen *et al.*, 2004; Sarzi-Puttini *et al.*, 2005; Dixon and Symmons, 2007; Popa *et al.*, 2007). TNF is an important contributor to the development of atherosclerotic lesions in that it induces proatherogenic changes in lipid metabolism and upregulates adhesion molecules, leading to the migration of monocytes into the vessel wall intima where they can become foam cells and form fatty streaks (Sarzi-Puttini *et al.*, 2005; Dixon and Symmons, 2007; Popa *et al.*, 2007). TNF may also increase collagen breakdown in the fibrous cap (via MMPs), which may lead to a plaque rupture. In addition, TNF has prothrombotic effects. Although TNFi therapy has been associated with an increase in high-density lipoprotein (HDL)-cholesterol in the short-term (weeks), this was not consistently accompanied by a favorable effect on the atherogenic index (Vis *et al.*, 2005; Popa *et al.*, 2007). It is currently unclear whether the

effects on the lipid profile persist and reduce atherogenesis in the long-term. RCTs of IFX and ETA in moderate to severe congestive heart failure (CHF) revealed that TNFi therapy did not improve the outcomes (clinical status, hospitalization, death), or was even detrimental (Chung *et al.*, 2003; Mann *et al.*, 2004).

Other special considerations

Due to possible infectious complications, TNFi and other biological agents are not recommended during the perioperative period of joint replacement and other (major) elective surgery (Saag *et al.*, 2008). It is, as yet, unclear whether TNFi treated RA patients are at increased risk of surgical site infections (da Cunha *et al.*, 2012). Live vaccines are contraindicated during biological therapy (Saag *et al.*, 2008; Repo and Peltomaa, 2012). In cases where such vaccines are needed, the biological agent should be suspended during the peri-vaccination period.

The approved TNFi agents are classified by the U.S. Food and Drug Administration (FDA) to the pregnancy risk category B, which means that 1) animal reproduction studies have failed to demonstrate a risk to the fetus, but there are no adequate and well-controlled studies of pregnant women; or 2) animal studies demonstrate a risk, and adequate and well-controlled studies in pregnant women have not been done during the first trimester (Law *et al.*, 2010). A recent SLR suggests that the overall risk of TNFi agents is relatively low; however, the data is insufficient to draw any firm conclusions (Bogas *et al.*, 2011). According to the current guidelines of the Finnish Society for Rheumatology, biological agents should be discontinued before planned pregnancy and are not recommended during breast-feeding (http://www.reumatologinenyhdistys.com/raskaus2009.pdf, accessed 8.8.2012).

5 INTRODUCTION AND BACKGROUND OF THE STUDY

The advent of biological drugs has significantly, even dramatically, improved the prognosis of rheumatoid arthritis (RA) in a substantial proportion of patients with moderate to severe active disease refractory to treatment with conventional disease modifying antirheumatic drugs (cDMARDs). Tumor necrosis factor inhibitors (TNFi) agents were the first biologicals to emerge at the turn of the century, and they are still the most widely used among this group of drugs. During the first decade of clinical use, almost 2 million patients with various immune-mediated inflammatory disorders were treated with these agents worldwide (Kerbleski and Gottlieb, 2009). Jönsson *et al.* (2008) estimated, based on data from 2006, that ca 9% of Finnish RA patients (ca 3200 patients) use TNFi agents; this point-estimate seems to have stayed nearly the same, around 10%, in more recent years. A timeline and statistics relating to the use of TNFi agents in Finland is presented in Table 9.

Table 9. Timeline and statistics relating to the use of anti-TNF agents in Finland, with focus on the years 2001, 2004, 2007 and 2010.

Year	Marketing authorizations[1] (MA), launches and reimbursability	Indications[2]	DDD / 1000 inhabitants / day[3]	No. of recipients of reimbursement[3,4]
1999	IFX MA 13.8.1999			
2000	ETA MA 3.2.2000 Initial problems with production capacity			
2001		IFX: RA, CD ETA: RA, JIA	IFX: 0.11 ETA: NA	0
2002	ETA reimbursable 1.12.2002			
2003	Re-launch of ETA[5] ADA MA 8.9.2003			
2004	ADA reimbursable 1.3.2004	IFX: RA, CD, AS ETA: RA, JIA, PsA ADA: RA	IFX: 0.22 ETA: 0.12 ADA: NA	1502
2007		IFX: RA, CD, AS, UC, PsA, plaque psoriasis ETA: RA, JIA, PsA, AS, plaque psoriasis ADA: RA, PsA, AS	IFX: 0.37 ETA: 0.27 ADA: 0.25	3371
2009	CER and GOL MA 1.10.2009			
2010	CER reimbursable 1.5.2010 GOL reimbursable 1.10.2010	IFX: RA, CD, AS, UC, PsA, plaque psoriasis, PCD ETA: RA, JIA, PsA, AS, plaque psoriasis, plaque psoriasis in children ADA: RA, PsA, AS, JIA, plaque psoriasis, CD CER: RA GOL: RA, PsA, AS	IFX: 0.53 ETA: 0.39 ADA: 0.46	4978

Abbreviations: ADA=adalimumab (Humira); AS=ankylosing spondylitis; CD=Crohn's disease; CER=certolizumab pegol (Cimzia); DDD=defined daily dose; ETA=etanercept (Enbrel); GOL=golimumab (Simponi); IFX=infliximab (Remicade); JIA=juvenile idiopathic arthritis; MA=marketing authorization; NA=not applicable/available; No.=number; PCD=pediatric Crohn's disease; PsA=psoriatic arthritis; RA=rheumatoid arthritis; UC=ulcerative colitis.
1) Data from the Fimea web database; 2) Data from Pharmaca Fennica (printed version); 3) Data from the Finnish Statistics on Medicines; 4) Based on reimbursement code 313 of the Social Insurance Institution of Finland (SII). The code pertains to medicinal products eligible for restricted basic refund, and is defined as: "etanercept, infliximab and other significant and expensive drugs used in the treatment of rheumatoid diseases" (2004); "adalimumab, anakinra and etanercept (rheumatoid diseases)" (2007); "adalimumab, anakinra, etanercept, golimumab (from 1.10.2010) and certolizumab pegol (from 1.5.2010) (rheumatoid diseases)" (2010). 5) Jönsson *et al.*, 2008.

The efficacy and safety of the biological drugs in RA and other rheumatological indications for which they are approved have been evaluated in randomized controlled trials (RCTs) usually of 3 to 12 months duration with strict inclusion and exclusion criteria to define the study population. In order to acquire information on the safety and effectiveness in "real-life" clinical settings, international recommendations have encouraged data collection into national long-term registers (Furst *et al.*, 2002; Braun *et al.*, 2003; Braun *et al.*, 2006; Furst *et al.*, 2007; Furst *et al.*, 2010). In 1999, with the first biological drug being launched in Finland, the Finnish Society for Rheumatology set up a national register of biological treatment, which has subsequently become known as ROB-FIN.

National Current Care guidelines for RA were first published in 1999; recommendations for the use of biological drugs (TNFi and anakinra) were included in the 2003 update. These stated that biological therapy is warranted if the patient suffers from severe and continuously active disease (swollen joint count (SJC) ≥ 6, tender joint count (TJC) ≥ 6, morning stiffness ≥ 45 min and/or erythrocyte sedimentation rate (ESR) ≥30 mm/h and/or C-reactive protein (CRP) ≥2.8 mg/dl) despite combination therapy with cDMARDs (including methotrexate (MTX) ≥ 15 mg/week) and low-dose oral glucocorticoid (GC) (e.g., FIN-RACo combination; Möttönen *et al*., 1999). Treatment response according to ACR50 criteria was recommended to be assessed three months after the commencement of the biological drug. The newest update of the guidelines (2009) does not include such specific recommendations, but clearly emphasizes the importance of early, effective treatment with the aim of reaching clinical remission within the first year. Patients who continue to have active disease despite treatment with MTX and combination therapy with cDMARDs are eligible for biological drug therapy, primarily with a TNFi agent.

The use of TNFi and other biological drugs has led to significant increases in the direct costs of treatment of RA and other inflammatory arthritides. According to the Finnish Statistics on Medicines (FSM), the average cost per patient receiving reimbursement based on reimbursement code 313 of the Social Insurance Institution of Finland (SII) (see Table 9) in the years 2004, 2007, and 2010 were 12 803 €, 13 075 €, and 12 327 €, respectively, the total costs being 19 231 000 €, 44 074 000 €, and 61 365 000 €, respectively; the cost of infliximab (IFX) is not included in these figures. For a person weighing 70 kg and receiving IFX 3 mg/kg (i.e., 210 mg) every eight weeks, the annual drug cost would be 8 652 € (according to calculations based on the wholesale price; Finnish Statistics on Medicines, 2010), except for the first year when the cost would be 10 649 € due to the loading dose. In addition, there is the cost of intravenous (i.v.) infusion, which in 2007 was estimated to be 212 € per administration (Virkki *et al.*, 2008). In comparison, the annual cost of low-dose (≤ 25 mg/week) MTX or hydroxychloroquine (HCQ) 300 mg daily is < 100 €, while that of, e.g., sulfasalazine (SSZ) 2 g daily is < 300 €, and that of leflunomide (LEF) 20 mg daily is < 1000 € (retail prices according to Pharmaca Fennica 2011). Rheumatology has become one of the most costly specialties in Finland with regard to pharmacological therapy. Already in 2005 rheumatologists prescribed drugs for an average of 220 000 € per prescriber, while the corresponding figure for all physicians was 75 000 € (Timo Klaukka, personal communication). In fact, TNFi agents bring about one of the highest medicinal expenditures in many (Western) coutries; in Finland for example, the top three medicinal expenditures in 2011 were due to ADA, IFX and ETA (Jönsson *et al.*, 2008; Bendtzen, 2012; Kurki and Heinonen, 2012). However, TNFi and other biological drugs have a potential to prevent negative long-term outcomes, such as disability and work incapacity (Sokka, 2009), whereby their direct costs may be offset by savings in indirect costs.

While the efficacy of the TNFi agents seems comparable on a patient-population level, it is currently not possible to predict the extent to which an individual patient will respond to TNFi treatment or specific agents (Buch *et al.*, 2004; Klaasen *et al.*, 2009). The TNFi agents are structurally different, and although they share the same target molecule, they seem to have different actions clinically, e.g., having a differential effect in certain other inflammatory conditions (e.g., Crohn's disease) and somewhat differing safety profiles (Tracey *et al.*, 2008). Some studies have indicated differences in their TNF binding characteristics; ability to bind lymphotoxin-α; and ability to induce complement-dependent cytotoxicity (Scallon *et al.*, 2002; Mpofu *et al.*, 2005; Mitoma *et al.*, 2008; Kaymakcalan *et*

al., 2009). Other factors which may lead to variability in clinical responses include genetic differences in the treated patients; antibody-mediated clearance of the TNFi agents; and different pharmacokinetic profiles (Lutt and Deodhar, 2008). In view of the differing characteristics, switching a TNFi agent to another may be efficacious in case of treatment failure with the initial one. On the other hand, several biological drugs not targeting TNF are now available. The updated consensus statement on biological agents for the treatment of rheumatic diseases states that the optimal treatment of TNFi refractory RA remains to be determined (Furst *et al.*, 2012).

6 AIMS OF THE STUDY

- To assess the medium- to long-term (2 to 5 years) effectiveness of TNFi therapy in RA (Study I)
- To assess the safety and tolerability of TNFi and anti-IL-1 therapy in the medium- to long-term (up to 5 years) in a routine-care setting (Study II)
- To assess the cost-effectiveness of IFX therapy in RA and factors affecting it (Study III)
- To assess the extent to which RA patients benefit from switching a first TNFi agent to another one (Study IV)

7 PATIENTS AND METHODS

7.1 The Finnish register of biological treatment, ROB-FIN

Patient data for the studies was obtained from the Finnish register of biological treatment (ROB-FIN). The ROB-FIN register was established by the Finnish Society for Rheumatology, with the aim of nationwide longitudinal follow-up of outcomes in adult patients with rheumatologic diseases treated with biological agents. The national guidelines for patient selection for biological treatment are presented in the Introduction and background of the study – section. ROB-FIN register data collection started in 1999 and is ongoing. The register is maintained with the approval from the Internal Medicine Ethics Committee of the Hospital District of Helsinki and Uusimaa, and the Office of the Data Protection Ombudsman (Tietosuojavaltuutetun toimisto). For patient enrollment into the register, informed consent is required. The refusal rate is estimated to be <5% of the patients (Heikki Valleala, personal communication).

Reporting to the register is voluntary and not restricted to specific medical specialties or care centers. The register data are provided on a prospective, regular basis using structured forms available via the web site of the Society. Reporting occurs at baseline before starting biological therapy, and at pre-specified intervals during therapy (at 3 and 6 months, and semiannually thereafter, coinciding with routine rheumatologic care) and on discontinuation of therapy. The centralized database input is funded by the pharmaceutical companies with biological drugs on the market in Finland (in alphabetical order, Abbott, Biovitrum, Bristol-Myers Squibb, Janssen, MSD, Pfizer, Roche, Schering-Plough, UCB, Wyeth). The research for the studies included in this thesis have been funded by unrestricted grants from foundations and pharmaceutical companies, and salary from the Ministry of Education and Culture via the National Doctoral Programme of Musculoskeletal Disorders and Biomaterials (TBDP) and the Ministry of Social Affairs and Health via the special state subsidy (EVO) for health science research (see Acknowledgements).

The data collected includes:

- patient demographics and background information (e.g., date of birth, sex, diagnosis, year of diagnosis, weight, height, and the presence/absence of RF, anti-cyclic citrullinated peptide (anti-CCP) positivity, HLA-B27 positivity, radiographic erosions, and sacroiliitis)
- the medications prescribed to the patient for the treatment of the rheumatologic disease (biological agent, NSAID, analgesic, GC, cDMARD), and the reason for eventual changes in the biological treatment
- the parameters needed for assessment of disease activity and response to treatment according to internationally adopted criteria (e.g., the ACR core set measures, DAS28 and EULAR response criteria)
- work capacity and resource utilization (patient-reported; added to the register in 2007)
- adverse events occurring during the treatment (description of the event, assessments of its severity and outcome).

The general inclusion criteria and numbers of patients of studies I to IV are presented in Table 10. Further details are given in the Results and discussion – section.

Table 10. Inclusion criteria and numbers of patients of studies I to IV.

	Study I (effectiveness)	**Study II (adverse events)**	**Study III (cost-effectiveness)**	**Study IV (TNFi switches)**
Reference	Nordström *et al.*, 2006	Konttinen *et al*., 2006	Virkki *et al.*, 2008	Virkki *et al.*, 2011
Rheumatologic diagnosis	RA	Any	RA	RA
First TNFi agent	IFX	Any*	IFX	Any
Baseline report required	Yes	No	Yes	No
Follow-up report required	No	Yes (AE)	Yes	Yes
Additional requirements	None	None	Baseline HAQ and patient's global assessment	Switch to a second TNFi agent; data on both treatments
No. of patients registered in ROB-FIN at the time of data extraction	1134 (RA 63%)	1440 (RA 61%)	2176 (RA 58%)	3145 (RA 54%)
No. of patients fulfilling the inclusion criteria of the study	364	248	297	479
Updated analyses	Yes (Study V), February 2012	Yes (Study V), April 2009	No	No

*) The biological drug was not required to be a TNFi agent.

7.2 Statistics

Data were analyzed with SPSS statistical software (versions 12 to 15; SPSS, Chicago, IL). The significance level was set at $p<0.05$ in all statistical testing. Two-tailed levels of significance were used throughout. Analyses were per protocol. Variable descriptives were checked for possible extreme values or errors in data input. Baseline demographics and disease characteristics were assessed using frequency calculations and descriptive statistics. Distributions of continuous variables were analyzed graphically and using statistical tests of normality (Kolmogorov-Smirnov or Shapiro-Wilk, as appropriate). Most of the continuous variables had skewed distributions and required nonparametric tests. In the case of ≥ 3 groups being compared, an overall test was performed prior to pairwise testing, which required a statistically significant overall result. Study I (effectiveness) contained many pairwise comparisons, and corrections for the multiple testing were made using the Bonferroni method. The following statistical methods were used, as appropriate:

- For group comparisons of categorical data: Chi-square, Cochran's Q, or McNemar's tests
- For related samples with a continuous scale: Friedman or Wilcoxon Signed-Rank tests

- For independent samples with a continuous scale were compared using Kruskal–Wallis or Mann–Whitney tests, as appropriate.

In addition, odds ratios were obtained from logistic regression, and survival analysis was performed using Kaplan–Meier plots and log-rank tests.

7.3 Additional methods and assessments

7.3.1 Study I

Response assessment considered changes in ACR core set measures and ACR response rates during IFX therapy. ACR response rate assessments focused on the ACR50 response after three months of IFX therapy, according to the 2003 National Current Care guidelines for RA (presented in the Introduction and background of the study – section), and on the ACR20 response after six months, which was compared to the primary endpoint of the ATTRACT study, i.e., the ACR20 response rate after 30 weeks of IFX with concomitant MTX (Maini *et al.*, 1999; the study is presented in the Review of the literature – section). Effectiveness of combination therapies of IFX and cDMARDs was assessed based on presence or absence of MTX, and presence or absence of other cDMARDs in addition to MTX. Medication assessments also considered changes in the use, and dose, of oral GC. Discontinuation rates of IFX were evaluated, and updated analyses also evaluated time-to-event by means of survival analyses of IFX and biological DMARD (bDMARD) treatment. Survival analyses were performed according to a scenario in which patients lost to follow-up were assumed to have continued therapy, and another in which they were assumed to have discontinued therapy. AEs occurring during IFX treatment were also assessed.

7.3.2 Study II

For the AE analyses, the reported AEs were classified into groups of similar events. The basis for the classification was the grouping used in the AE report form[2]. If several signs and symptoms of an AE were reported, only the overruling main event was used for the statistical analyses. The classification of the AE seriousness was done at the discretion of the physician reporting the event. The predefined classes correspond to those used in reporting AEs to the Finnish Medicines Agency (Fimea), and are specified as mild, moderate, serious, life-threatening, fatal; anomaly; disablement; malignancy; and prolonged hospitalization. Serious AEs (SAEs) include those that require hospitalization or intervention to prevent life-threatening illness or injury or permanent impairment, but can also comprise other important medical events (web sites of the European Medicines Agency[3] and FDA[4]). Therefore, in the present study, all cases of tuberculosis (TB), septicaemia and AEs leading to hospitalization were classified as serious irrespective of the classification in the report (missing or not classified as a SAE); such AEs included cerebral infarction, cerebral hemorrhage, pulmonary embolism, myocardial infarction, heart failure

[2]http://www.reumatologinenyhdistys.fi/files/robfin_haittavaikutusilmoitus3_02022007.pdf, accessed 16.3.2014

[3]http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf, accessed 30.12.2013

[4]http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm, accessed 30.12.2013

(in a patient who required an artificial pacemaker), and hemiplegia. In the present study, cancers are classified separately from these SAEs. Incidence rates of cancers among the ROB-FIN cohort were compared with those of the Finnish general population (men and women over the age of 15 years) using data from the Finnish Cancer Registry and by calculating standardized incidence ratios (SIR).

7.3.3 Study III

Functional disability has been found to be the strongest predictor of cost in RA (Kavanaugh, 2005). Treatments that improve functional status therefore have the potential to lower the costs of the disease. Moreover, improvement in functional status correlates with improvement in quality of life, which is also affected by the level of disease activity (Kavanaugh, 2005; Kobelt *et al.*, 2005). Health-related quality of life can be quantified using health state classification instruments, which have been presented in the literature review section. These yield values of utility, usually ranging from 0 to 1, which correspond to the weight associated with a particular health state. These weights can be used to calculate quality-adjusted life years (QALYs); this is done by multiplying the utility score associated with a particular health state by the duration of time spent in that health state. In the present study, a cost-utility analysis (CUA) was performed in which utility scores were appointed according to Kobelt *et al.* (2005). The scores were derived from the EQ-5D health state classification instrument and related to HAQ score and patient's global assessment of disease activity using multiple regression. They are based on a survey of 616 RA patients, carried out in 2002 by the department of rheumatology at Malmö University Hospital in Sweden. In the present study, QALYs were calculated based on these utilities (Table 11), using patient-level data up to the last visit registered in ROB-FIN.

Table 11. Utilities by functional state and disease activity, ascribed by Kobelt *et al.* (2005).

HAQ score	Utility when global VAS <40 mm	Utility when global VAS ≥40 mm
<0.6	0.780	0.709
0.6 to <1.1	0.704	0.568
1.1 to <1.6	0.676	0.441
1.6 to <2.1	0.562	0.446
≥2.1	0.408	0.213

VAS=visual analogue scale

The following assumptions were made prior to calculation of changes in QALYs resulting from IFX therapy: IFX therapy was added to an ongoing cDMARD therapy, which had been optimized for the individual patient, but which had not led to a satisfactory response; the effect onset of IFX was assumed to occur two weeks after the commencement (Maini *et al.*, 1999); and, had the patient not started IFX, he/she would have continued cDMARD therapy with the patient's global assessment remaining at the baseline level and the HAQ score progressing 0.031 units/year (Scott *et al.*, 2000). The costs considered were direct medical costs as follows: cost of IFX 622.22 €/100 mg, and cost of i.v. infusion 211.73 €/administration (used in the correspondence with national drug pricing and reimbursement authorities; Schering-Plough, personal communication, 2007). Patient-level costs were

calculated based on dose and dosage frequency, and they were related to the change in QALYs resulting from IFX therapy. Discounting was not performed. A cost of ≤40,000 € per QALY gained was considered cost effective (Rawlins and Culyer, 2004; Maetzel, 2005). Patient characteristics, baseline disease status, IFX dose, use of concomitant MTX, and the magnitude of response, in terms of HAQ, global VAS, DAS28 and ACR50, were compared among the subgroups with a cost per QALY gained of ≤40,000 € or >40,000 €, or with no QALY benefit.

7.3.4 Study IV

Reasons for switching were classified as follows: (1) lack of effectiveness (LOE), (2) AE, and (3) other reasons (known or unknown reasons, which may include nonmedical ones such as reimbursement or patient preference). In practice, switching due to LOE occurs at the discretion of the attending rheumatologist, i.e., taking into account the effect of the drug and the needs of the patient. According to the 2003 National Current Care guidelines for RA, ACR50 response at three months of TNFi therapy warrants treatment continuation. Therefore, switching due to LOE was assumed in the following cases: (1) if LOE was reported by the attending rheumatologist as the reason for the switch, or (2) if the reason for switching was not reported, but ACR50 response was not achieved (primary LOE) or had been lost (secondary LOE). The effectiveness of switching was assessed based on SJC, CRP, DAS28, and ACR50 response. The studied time points were, for the first TNFi agent, the baseline and 3 months, best and last observations during treatment; and for the second TNFi agent, the 3 months, best and last observations. Survival analysis was performed on the treatment duration of the second TNFi agent, with the end points being discontinuation due to LOE or AE.

7.3.5 Cancer incidence assessments

Data concerning cancers diagnosed in ROB-FIN registered RA patients was obtained from the Finnish Cancer Registry (FCR), with permission from the National Institute for Health and Welfare. The FCR was founded in 1952, and has since maintained a nationwide database covering > 99% of all cancers diagnosed in Finland (Teppo *et al.*, 1994; Pukkala *et al.*, 2011). In the present study, standardized incidence ratios (SIR) were calculated in order to compare cancer incidences from 2002 through 2008 in RA patients during or within one year after anti-TNF therapy, with those in the Finnish adult population (age ≥ 15 years). The RA patients were followed up from 1.1.2002 or from a later baseline visit. The follow-up ended at the date of cancer diagnosis or, in patients not diagnosed with cancer, one year after the last registered visit or 31.12.2008 (whichever occurred first); eventual deaths occurring during the extension period were not accounted for. SIR calculations were performed for cancer overall and site-specifically for cancers that were diagnosed in >1 RA patient. Patients diagnosed with cancer before starting TNFi treatment were not excluded from the analyses. Cancer rates in the Finnish adult population were obtained from the statistical yearbooks published by the FCR; rates in the years 2002, 2005, and 2008 were averaged. 95% confidence intervals were calculated using Clinstat statistical software.

8 RESULTS AND DISCUSSION

8.1 Reporting to the ROB-FIN register and trends in anti-TNF use (V)

By February 2012, roughly 25 500 ROB-FIN register reports had been filed concerning 4 834 patients, 54% of whom had RA. The number of registered patients has grown steadily by a mean of ca 400 each year (Figure 3).

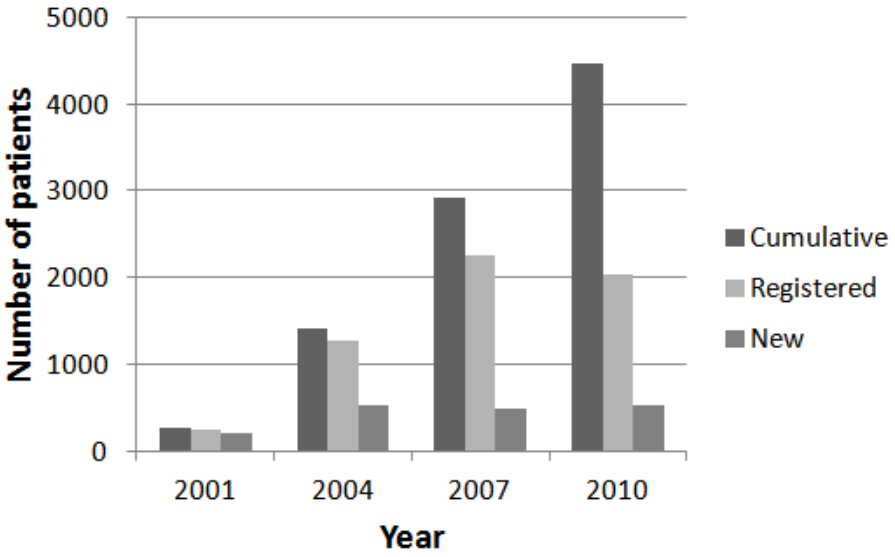

Figure 3. Numbers of cumulative, registered, and new patients, respectively, in the ROB-FIN register in the years 2001, 2004, 2007 and 2010 (all diagnoses and biological agents included).

Overall, reports were sent from 16 of 21 hospital district areas covering roughly 80% of the Finnish population; annually, reports came from ca two-thirds of the districts. Reports mostly came from central and regional hospitals, but also other units, such as city hospitals. In addition, reports were sent from the Rheumatism Foundation Hospital in Heinola, where patients from various parts of the country were treated. Overall, nearly 300 physicians reported to the register, indicating that, in addition to rheumatologists, also other specialists or specialists in training were involved in the management and documentation of rheumatology patients using biologicals (the number of rheumatologists in Finland is ca 140, roughly half of whom work as attending rheumatologists; Luosujärvi, 2006).

Figure 4 shows the numbers and proportions of patients starting treatment with various TNFi agents in the years 2001 to 2010. The notable increase by the year 2004 was, presumably, due to the availability of guidelines for their use and the increased experience with this type of drugs, as well as the availability of self-injectable, reimbursed drug options.

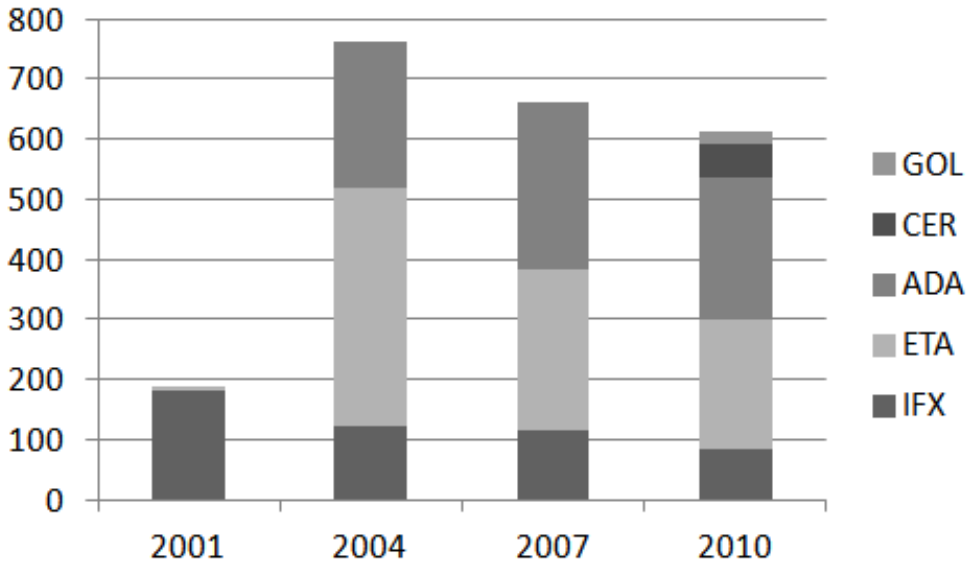

Figure 4. Numbers and proportions of ROB-FIN registered patients starting various TNFi agents in the years 2001, 2004, 2007 and 2010 (all diagnoses included). Of all registered patients, 1392 had been treated with IFX, 2344 with ETA, 2117 with ADA, 90 with CER, and 111 with GOL. GOL=golimumab; CER=certolizumab pegol; ADA=adalimumab; ETA=etanercept; IFX=infliximab.

Table 12 shows the numbers of TNFi treated, ROB-FIN registered patients and the coverage of the SII code 313 reimbursed patients and of the defined daily doses (DDDs) of TNFi agents consumed in Finland in the years 2001 to 2010. The DDDs encompass all indications of use, including rheumatological disorders in adults, juvenile idiopathic arthritis (JIA), Crohn's disease (CD), ulcerative colitis (UC), and plaque psoriasis.

Table 12. The number of TNFi treated, ROB-FIN registered patients (all diagnoses included); proportion of SII code 313 reimbursed patients who were registered in ROB-FIN; and proportion of the defined daily doses (DDDs) of IFX, etanercept (ETA), and adalimumab (ADA) consumed in Finland covered in the ROB-FIN register, in the years 2001, 2004, 2007, and 2010.

Year	TNFi treated patients in ROB-FIN	Proportion of SII 313 reimbursed patients	Proportion of DDDs of IFX	Proportion of DDDs of ETA	Proportion of DDDs of ADA
2001	247	NA	23%	NA	NA
2004	1239	62%	32%	50%	NA
2007	2129	51%	21%	48%	39%
2010	1734	29%	8%	19%	16%

NA=not applicable

The DDD coverage is lower for IFX than for ETA and ADA, which may be due to the higher recommended dose of IFX in the treatment of CD and psoriasis (5 mg/kg, as opposed to 3 mg/kg in the treatment of RA). The number of patients with pediatric or non-rheumatological indications could be estimated to have been in the order of 1000 in the year 2010 (FSM; Tynjälä *et al*., 2009; Jussila *et al*., 2011). ROB-FIN may be estimated to have encompassed ca 60% of all Finnish adult patients with rheumatological indications using biological drugs in the mid-2000s, and around one-third in the later part of the decade. The coverage in the reporting hospital distric areas is higher compared with the nationwide estimate (ca 94% in 2004, and 44% in 2010, assuming two-thirds of the patients were from such areas). The follow-up is prospective, and no apparent documentation bias is evident. Taken together, it would seem that the patients registered in ROB-FIN make up a representative sample of the Finnish RA patients who use biological drugs.

The smaller coverage of register data from 2010 (compared with, e.g., 2004 and 2007) may, to some extent, be explained by the lag-time in the register data obtainability. However, it is also supposedly due to the considerable increase in the number of patients being treated with biological agents, whereby more effective means of data collection is called for. While the ROB-FIN paper forms can be used in the patient monitoring in the clinics, the electronic data acquisition provides even better tools through graphs and other data summaries; this type of monitoring of treatment response in individual patients may reinforce voluntary reporting to registers (Hetland, 2005). Clinical information software (GoTreatIT) is currently being implemented in several Finnish rheumatology units, and data obtained in this way may be incorporated to the ROB-FIN register in the near future.

In accordance with earlier observations (Kvien *et al.*, 2001; Kvien *et al*., 2003; Sokka and Pincus, 2003; Zink *et al*., 2006), it appeared that even less than one-tenth of ROB-FIN patients starting TNFi therapy would fulfil the selection criteria of RCTs. The general criteria of the ATTRACT trial (i.e., SJC $\geq$ 6, TJC $\geq$ 6, and two of the following: morning stiffness $\geq$ 45 minutes, ESR > 28 mm/h, and CRP > 2 mg/dl; concomitant MTX required but no other cDMARDs allowed; prednisone-equivalent daily dose of oral GC not exceeding 10 mg) (Maini *et al*., 1999) were fulfilled by only 9% of the RA patients (Table 13; the figures are crude estimates as 1) duration of morning stiffness is not assessed in ROB-FIN and was assumed to be a fulfilled criterion in the analysis, and 2) ATTRACT and most other RCTs have used a 66 SJC and 68 TJC index, while ROB-FIN uses a 54 SJC and 53 TJC index). Application of more stringent criteria of other RCTs (e.g., higher required joint counts) would reduce the proportion further.

Table 13. Proportion of ROB-FIN registered RA patients fulfilling the general selection criteria of the ATTRACT trial (see text) during various time periods and overall, and period-wise comparisons of disease activity, disease duration, and age of RA patients starting treatment with a TNFi agent (n=1614).

Period	Proportion fulfilling the general disease activity and medication criteria of the ATTRACT trial	Proportion fulfilling the disease activity criteria of the ATTRACT trial	Proportion fulfilling the medication criteria of the ATTRACT trial	DAS28 score, median (IQR)	Disease duration (years), median	Proportion with early RA (≤ 3 years)	Age (years), median
1999 to 2002 (n=288)	20%	56%	37%	NA	12	10%	50
2003 to 2006 (n=794)	8%	38%	19%	5.1 (4.2 to 5.7)	11	16%	54
2007 to 2011 (n=532)	5%	25%	19%	4.8 (3.7 to 5.6)	9	28%	55
Overall (n=1614)	9%	37%	22%	NA	NA	NA	NA

IQR=interquartile range; NA=not assessed

The disease activity of RA patients starting TNFi therapy has decreased through the years ($p<0.001$), but remains on a high or moderate level (Table 13). The disease duration (assessed as time since diagnosis) has decreased ($p<0.001$). However, the age at commencement has increased somewhat ($p<0.001$). Similar trends have been observed in other European countries, i.e., the baseline disease activity has decreased and age increased, and an increasing proportion of the patients is treated with TNFi agents relatively early (within a few years) in the disease course (Hetland *et al*., 2008; Söderlin and Geborek, 2008; Hyrich *et al*., 2011; Gómez-Reino *et al*., 2012). Despite the finding of older age at baseline, there has not been evidence of increased comorbidity (Hyrich *et al*., 2011; Gómez-Reino *et al*., 2012).

8.2 Effectiveness and safety of infliximab therapy in the treatment of RA (I, V)

8.2.1 Effectiveness of infliximab in RA patients treated with concomitant methotrexate and other conventional disease modifying antirheumatic drugs (I)

At the time of the analyses performed for Study I (Nordström *et al.*, 2006), ROB-FIN encompassed 436 patients with RA who had received IFX at least once in the time period between May 1999 and September 2004, and who had not used bDMARDs earlier. The requirement of a filed baseline report was fulfilled in 364 cases, and these patients made up

the study cohort. The mean age of the patients was 49 years (range 18 to 77 years), and 253 (70%) were women. Two-thirds had a seropositive disease. The patients had moderate to severe disease at baseline (Table 14). Most patients had long-standing disease; the median time since diagnosis was 11 years (range 0 to 47 years). 28 of 254 patients with reported disease duration had been diagnosed ≤ 3 years earlier.

Table 14. ACR core set measures in the cohort of IFX treated RA patients (n=364) at baseline, after three months on IFX, and at the last observation of biological therapy (IFX or other) (3 months IFX *vs.* baseline, p<0.001; last observation *vs.* baseline, p<0.001).

	Baseline			**3 months IFX[b,c]**			**Last observation (IFX or other bDMARD)**		
	Median	IQR	n	Median	IQR	n	Median	IQR	n
SJC	10	6 to 17	353	2	1 to 6	258	1	0 to 4	352
TJC	11	6 to 19	337	3	1 to 8	248	2	0 to 5	351
CRP (mg/dl)	3.2	1.3 to 6.2	352	1.0	0.5 to 2.7	260	0.6	0.4 to 1.6	349
ESR (mm/h)	35	19 to 58	349	18	9 to 36	258	16	7 to 30	348
Patient's global (mm VAS)	65	48 to 78	318	25	12 to 50	240	29	13 to 55	349
Pain (mm VAS)	65	44 to 80	322	26	11 to 53	245	30	14 to 55	348
Doctor's global (mm VAS[a])	75	50 to 75	304	25	25 to 50	227	18	7 to 34	326
HAQ score	1.3	0.8 to 1.9	322	0.9	0.3 to 1.4	253	1.0	0.4 to 1.5	335

IQR=interquartile range, n=number of patients. a) Up to year 2004, register forms had a 5-grade Likert scale, which has been converted to 100 mm VAS as follows: grade 1, 0 mm; grade 2, 25 mm; grade 3, 50 mm; grade 4, 75 mm; grade 5, 100 mm. b) At the time of analysis, 323 patients had used IFX for at least three months. Included in this assessment are the patients with reported data from the 3 months visit. c) These values persisted throughout the follow-up in the patients who remained on IFX.

At baseline, 95% used a concomitant cDMARD and 86% used oral GC; combination therapy with two or more concomitant cDMARDs was common, used in 44%. Only 68% used MTX; of the MTX users, 30% used HCQ and 21% used SSZ, which suggests that the FIN-RACo combination was not very widely used in this setting. Patients who did not use MTX most frequently used leflunomide (31%) or azathioprine (22%). cDMARD usage remained stable during the 24 month follow-up (no statistically significant changes), while oral GC usage decreased. At 12 and 24 months after commencement of IFX, 79% and 67% used oral GC, respectively. In GC users, GC doses were reduced within the first months of IFX therapy, from a median prednisone-equivalent daily dose of 7.5 mg at baseline to 5.0 mg at three months and thereafter (p<0.001). By three months, 41% of the patients had discontinued usage of NSAIDs, while only 4% had started usage.

The ACR20 and ACR50 response rates at three months after commencement of IFX were 64% (144/225) and 41% (92/225), respectively. Sub-analyses of ACR response rates in groups of patients who used concomitant MTX, but no other cDMARDs (IFX+MTX group), MTX and SSZ (± other cDMARDs) (IFX+MTX+SSZ group), and cDMARDs other than MTX (IFX+non-MTX group), were performed. Oral GC use among these groups was similar (p=0.33 at baseline, p=0.22 after three months). The IFX+MTX+SSZ group tended to have smaller values of baseline ACR core set measures; the differences in TJC

and HAQ score were statistically significant between the IFX+MTX+SSZ group and the IFX+non-MTX group (TJC median 6 *vs.* 14, HAQ score median 1.0 *vs.* 1.6; both $p<0.05$). The ACR20 and ACR50 response rates at three months in the subgroups are presented in Table 15. The differences between the groups were not statistically significant.

Table 15. ACR20 and ACR50 response rates at three months after commencement of IFX. At the time of analysis, 314 of the 364 patients in the cohort had used IFX for at least three months; the numbers of assessable patients, i.e., with sufficient reported data from the three months visit, are given in parentheses. For definitions of drug combinations, see text.

	IFX overall	IFX+MTX	IFX+MTX+SSZ	IFX+non-MTX
ACR20	**64%** (144/225)	**71%** (48/68)	**71%** (22/31)	**63%** (37/59)
ACR50	**41%** (92/225)	**44%** (30/68)	**52%** (16/31)	**32%** (19/59)

The ACR20 response rate at six months in the IFX+MTX group was 65% (42/65), and was in accordance with that of IFX standard dosage (3 mg/kg at weeks 0, 2, and 6, and thereafter every eight weeks) with concomitant MTX in the ATTRACT trial; 50% of the patients in the trial reached the primary endpoint of ACR20 response at 30 weeks (Maini *et al*., 1999). The per protocol analysis used in the current study may inflate the response rate relative to that obtained through intention-to-treat analysis. Assuming discontinuers to be ACR20 non-responders yields response rates closely approximating that of the ATTRACT trial. It is also possible that the open setting, where the patient and doctor are aware of the treatment given, affects the response rate. For example, greater responses in open settings, compared with RCTs, have also been found for ankylosing spondylitis (AS), e.g., when using the Assessment in Ankylosing Spondylitis Response Criteria (ASAS) which, similar to the ACR response criteria, include pain and global assessments as patient reported outcome measures (Breban *et al*., 2002; Temekonidis *et al*., 2003; Konttinen *et al*., 2007). Moreover, the routine care setting allows for individual treatment adjustments as needed, whereas rigid treatment protocols are applied in RCTs; however, decreases in GC and NSAID usage occurred more frequently than increases in the cohort patients, while cDMARD use remained relatively stable.

The slightly better response rate in the observational cohort could also, perhaps, be explained by differences in the extent to which complete, but time consuming, joint counts are performed in the RCT and routine care settings. A separate register-based study of the SJCs of 86 RA patients treated with TNFi agents (mainly ETA and ADA) at the Helsinki University Surgical Hospital indicated that the metatarsophalangeal joints (MTPs) tended to improve to a greater extent than other joint areas (improvement after two to six months in 96% of MTPs *vs.* 65% to 78% of metacarpophalangeal joints (MCPs), proximal interphalangeal joints (PIPs), wrists, elbows, and ankles, $p<0.001$; 88% of knees, $p=0.09$) (unpublished data). This could indicate thorough baseline, but more pragmatic follow-up assessments in which the thoroughness of the assessment of the MTPs partly depends on whether these joints pose a problem for the patient (Heikki Valleala, personal communication). Calculation of ACR response rates using 28 joint count indices might lead to better consistency in the observational setting.

8.2.2 Adverse events of infliximab in RA patients treated with concomitant methotrexate and other conventional disease modifying antirheumatic drugs (I)

The safety profiles appeared to be similar among groups of RA patients using IFX with various concomitant cDMARDs (assessed in the 436 patients who had received IFX at least once in the time period between May 1999 and September 2004 and whose data were extracted for Study I). Reported SAEs were, among 199 patients exposed to IFX+MTX, one each of infusion reaction, pancreatitis, an unspecified SAE, and a fatal myocardial infarction; among 68 patients exposed to IFX+MTX+SSZ, again one each, erysipelas and a life-threatening pneumonia; and among 142 patients exposed to IFX+non-MTX, five infections, two infusion reactions, and two eczemas. Four cancers were reported: one meningeoma in an IFX+MTX treated patient, and three breast cancers in IFX+non-MTX treated patients.

8.2.3 Updated analysis of the cohort of RA patients treated with infliximab (V)

An updated analysis of the original cohort of 364 IFX treated RA patients (hereafter denoted the original IFX cohort) was performed based on register data obtained in February 2012. At that time, the mean follow-up time of IFX was 2.4 years (median 1.3 years, range 0 to 11.2 years), and that of biological therapy was 5.4 years (median 6.0 years, range 0 to 11.2 years). The patients had used a mean of two biological drugs (range one to six); 203 (56%) of the patients had switched IFX to another biological drug, and 105 (29%) had used > 2 biological drugs.

Of the 364 patients, 93 (26%) had discontinued IFX due to lack or loss of effectiveness (LOE), 53 (15%) due to AEs, four (1%) due to remission, and 100 (28%) due to other or unspecified reasons. 15 (4%) patients were still using IFX, but 99 (27%) had been lost to follow-up (defined here as no reports after 31.12.2010). At the last observation of biological therapy (IFX or other) most the patients had relatively low disease activity (Table 14). 113 of 254 assessable patients (45%) were in DAS28 remission (DAS28 score < 2.6). IFX and bDMARD survival, with any reason for discontinuation during up to five years of treatment as the end-point, is presented in Figure 5.

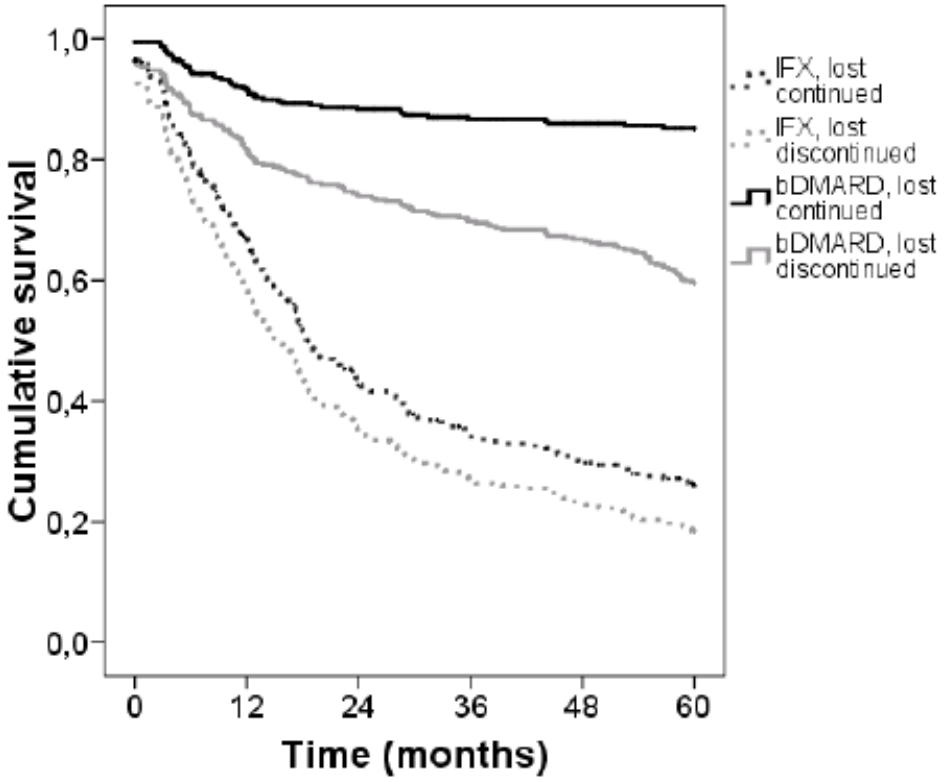

Figure 5. IFX and bDMARD survival in the cohort of IFX treated RA patients (n=364), with any reason for discontinuation during up to five years of treatment as the end-point. bDMARD refers to treatment with any biological agent, i.e., IFX or subsequent other drug. Black solid line: bDMARD survival, with patients lost to follow-up assumed to have continued treatment; gray solid line: bDMARD survival, with patients lost to follow-up assumed to have discontinued treatment; black dotted line: IFX survival, with patients lost to follow-up assumed to have continued treatment; gray dotted line: IFX survival, with patients lost to follow-up assumed to have discontinued treatment.

The overall persistence of IFX treatment in the original cohort seems to be somewhat lower than that seen in other observational cohorts. Data from the British BSRBR revealed treatment persistence rates of the first TNFi therapy (IFX, ETA or ADA) of 71% at one year, 50% at two years, and 42% at five years (Soliman *et al*., 2011). Data from the Danish DANBIO register revealed the persistence rate of IFX at four years to be 41%, while that of ETA was 56% and that of ADA was 52% (Hetland *et al*., 2010). In that study, the lower persistence of IFX was mainly due to AEs (hazard ratio (HR) 2.7 compared with ETA, and 1.8 compared with ADA), but also due to LOE (HR 1.7 compared with ETA, and 1.2 compared with ADA). The discontinuation rates due to LOE and AEs in the original IFX cohort appear comparable with other observational cohorts (Curtis *et al.*, 2010). In the study by Gómez-Reino *et al*. (2012), ca 7% discontinued their first TNFi agent during the first year of treatment due to LOE in 2000 to 2003, while in more recent years the percentage has increased to ca 12%. In the same study, the discontinuation rate due to AEs has remained stable at just under 10%. In the study by Soliman *et al*. (2011), with median follow-up time of two years, 22% of the patients had discontinued their first TNFi therapy due to LOE, and 21% due to AEs. It appears that other or unspecified reasons for

discontinuing IFX in the original cohort are comparatively large. The unspecified reasons may include nonmedical ones such as reimbursement or patient preference. Naturally, concomitant reasons for discontinuation may exist, whereby, e.g., better effectiveness is sought, despite, e.g., achievement of an ACR50 response and relatively low level of disease activity.

The updated analysis of the original IFX cohort rendered ACR20, ACR50, and ACR70 response rates at three months of 62% (n=148 of 237 assessable), 40% (n=95) and 17% (n=39), respectively. The rates were consistent with the "60-40-20" rule described in the review of the literature (Chi-square goodness-of-fit test, p=0.44, p=0.98, and p=0.17, respectively). Individual ACR core set measures at three months are shown in Table 14. The response achieved at 3 months was indicative of the subsequent probability of response, at least in those who responded to the treatment. For instance, an ACR50 response achieved at three months was maintained up to two years in ca two-thirds of the patients. However, nearly half of the patients (48%) who were ACR50 non-responders at three months, but continued treatment with IFX, achieved this response at some time during the two year follow-up. These findings are consistent with those of pooled analyses of ROB-FIN data of biological therapies (mainly TNFi agents) (Virkki *et al*., 2010). Therefore, it appears that continuation of TNFi therapy may be beneficial even if a significant response is not achieved within the first few months. Findings from the TEMPO trial of ETA lend support for this notion (Kavanaugh *et al*., 2008). In that trial, up to half of the non- and partial responders at week 12 showed improved ACR responses at week 24 in all treatment arms (ETA, MTX, or ETA+MTX), while less than one-fourth showed a decreased response (≤10% in the ETA+MTX arm). The 24 week response was maintained in the majority of patients up to 52 weeks (>80% in the ETA+MTX arm). Importantly, in the ETA arms, a delayed response was not associated with increased radiographic progression at week 52 (radiological outcomes are not available in the ROB-FIN register). Based on several RCTs, clinical responses appear to level off after six months of treatment (Bathon *et al*., 2000; Keystone *et al*., 2004b; Klareskog *et al*., 2004; Emery *et al*., 2008). Therefore, three to six months may be an appropriate treatment trial duration, provided the patient tolerates the drug.

The magnitude of baseline disease activity, assessed through SJC, CRP, and patient's global assessment, correlated significantly with the magnitude of absolute improvement of the respective parameters ($p<0.001$). However, the relative degrees of improvement, as assessed by ACR20, ACR50, and ACR70 response rates at three months, were not dependent on the magnitude of baseline disease activity. Some observational studies have indicated that treatment responses, including ACR response rates, DAS28 improvement, EULAR response and remission rates, have improved, simultaneously with the trend toward starting TNFi treatment earlier in the disease course and in less severe disease (Hetland *et al*., 2008; Hyrich *et al*., 2011). The trend toward lower baseline disease activity implies a possibility of remission being achieved more frequently, if indeed the relative improvement remains at an unchanged level or is improved.

Taken together, Study I and its updated results imply that IFX can be added to ongoing combination cDMARD therapy (e.g., FIN-RACo combination; Möttönen *et al*., 1999) or even cDMARDs other than MTX, e.g., in patients who do not tolerate MTX. The effectiveness of these combinations appears to be comparable. However, the possibly increased risk of developing SAEs and/or human anti-chimeric antibodies (HACAs) among patients not using concomitant MTX remains elusive and is difficult to assess in a non-

randomized setting. Interestingly, data from the British Society for Rheumatology Biologics Register (BSRBR) indicated that, compared with patients using TNFi combined with MTX as the sole cDMARD, patients using TNFi in combination with MTX plus SSZ and/or HCQ were less likely to discontinue their first TNFi therapy due to inefficacy or AEs (Soliman *et al*., 2011). Conversely, patients using TNFi in combination with SSZ or LEF monotherapy, or not using concomitant cDMARDs, were more likely to discontinue their first TNFi therapy due to inefficacy or AEs. The reason for this remained speculative in that it may be affected by unmeasured confounders, such as a generally better drug tolerability of the patients using cDMARD combinations.

8.2.4 Pooled analyses of ROB-FIN data of biological therapies

Pooled analyses of ROB-FIN data on the effectiveness of biological therapies for the treatment of RA rendered ACR20, ACR50, and ACR70 response rates at three months of 65% (n=440 of 673), 41% (n=277), and 20% (n=136), respectively (Virkki *et al*., 2010). No statistically significant differences in the rates were found among the biological agents assessed (IFX, ETA, ADA, anakinra, rituximab). The efficacy of the TNFi agents appears comparable also based on indirect comparisons and meta-analyses of RCTs (Hochberg *et al*., 2003; Gartlehner *et al*., 2006). However, observational data from the Danish DANBIO register indicate that differences between the agents may exist in practice (Hetland *et al*., 2010). In that study, ADA had the highest treatment response rate and ETA had the longest treatment persistence rate, while IFX had the lowest rates. Of the three agents ETA was discontinued least frequently due to AEs. Our meta-analysis of RCTs also lends support to the notion that ETA perhaps is the safest alternative of the currently available TNFi agents (Aaltonen *et al*., 2012).

The pooled ROB-FIN analyses yielded an improvement in the DAS28 score of an average of 1.8 at three months after commencement of bDMARD therapy. A clinically significant improvement of >1.2 was achieved by 69% of the patients (n=399 of 577 assessable). At baseline, 6% (n=36) of the patients had a low DAS28 score (<3.2), and 2% (n=12) were in DAS28 remission (<2.6); after three months, the corresponding proportions were 49% (n=285) and 33% (n=189), respectively. Within one, two and three years, DAS28 remission had been achieved by 42%, 50% and 55%, respectively.

At the time of analysis, the mean follow-up time of the RA patients was 2.3 years (range 0.0 to 8.8 years). During that time, the first bDMARD had been discontinued by 17% due to LOE and 10% due to AEs, usually within the first year. bDMARD switches were common, occurring in more than one-third for various reasons.

8.3 Adverse events of anti-TNF therapy in a routine-care setting (II, V)

At the time of the analyses performed for Study II (Konttinen *et al*., 2006), ROB-FIN encompassed 1 440 patients (61% with RA) who had received a biological drug at least once up to March 2005. During a period of five years 308 AE reports concerning 248 patients had been filed, corresponding to 17% of all registered patients. This proportion was the same in an updated analysis on data obtained in April 2009, in which AEs had been

reported for 525 of the total of 3145 registered patients (hereafter denoted the total cohort). The mean follow-up time of the total cohort was 2.1 years (range 0.0 to 8.5 years). IFX had been used by 1127 patients, ETA by 1585, ADA by 1338, and anakinra by 98; other biological drugs had been used less frequently at the time of analysis. While all reported AEs for all biological agents have been included in the analyses, only the four mentioned have been statistically compared. Here, the focus will be mainly on the updates analyses, since the AEs reported by Konttinen *et al*. (2006) are included in these as well, and since the findings regarding, e.g., the most commonly reported AEs and those leading to treatment discontinuations remain the same. However, more information about rarer events (SAEs) has accrued, and the larger numbers of patients using various biological agents enable more statistical comparisons to be performed.

Figure 6 shows the percentages of the reported AEs according to the updated analysis, classified according to type or site of the event. AEs led to discontinuation of the bDMARD in 290 patients, i.e., 9% of the total cohort.

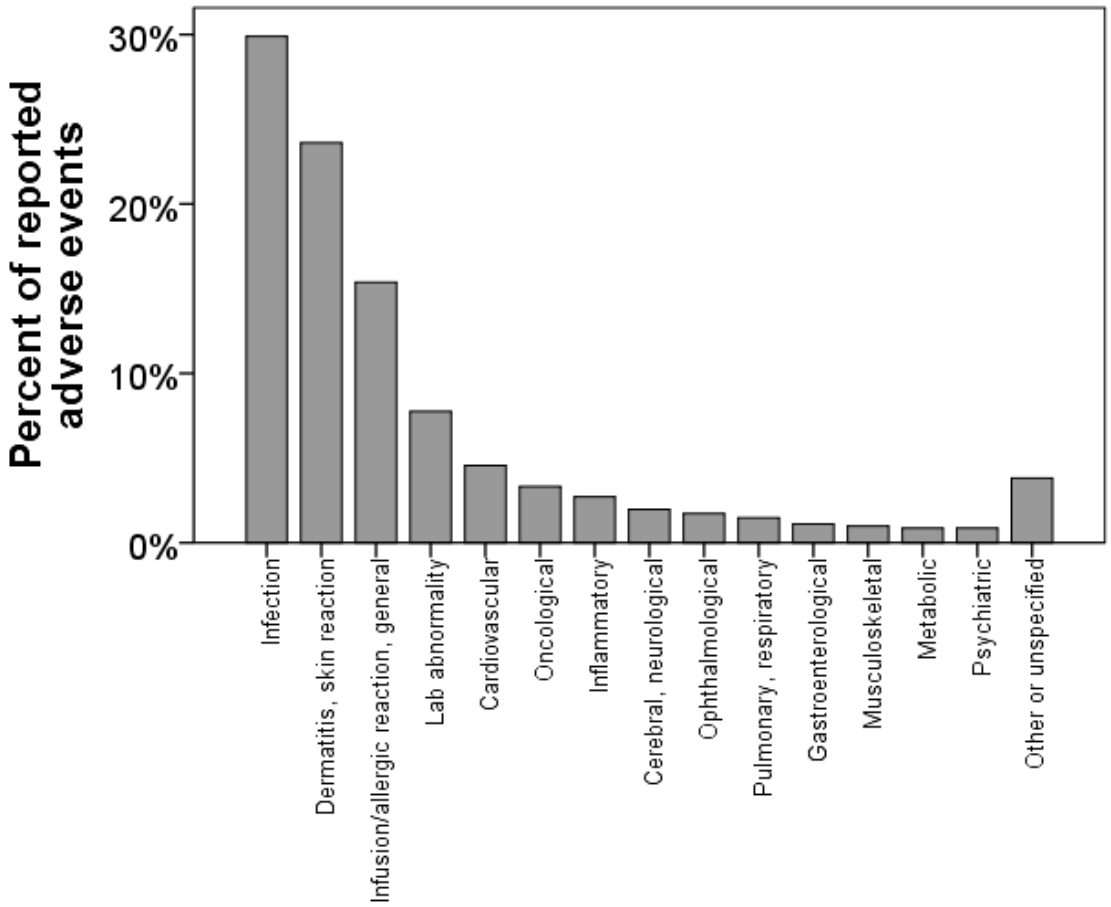

Figure 6. Percentages of the reported adverse events (n=813), classified according to type or site of the event. These AEs concerned 525 of the total of 3145 ROB-FIN registered patients. "General" refers to general symptoms (see text for further details).

8.3.1 Most frequent adverse events (II, V)

Infections (II, V)

A total of 238 reports concerning various infections in 194 patients were reported; this corresponded to 6.2% of the total cohort. The mean time to the occurrence of the first infection was 11.5 months (median 8.3 months, range 0.1 to 59 months). Several observational studies and a meta-analysis of RCTs have indicated an increased risk of various (serious) infections during the first few months of TNFi therapy (Wallis *et al.*, 2004; Dixon *et al.*, 2006; Dixon *et al.*, 2007; Leombruno *et al.*, 2009). This could be due to, e.g., use of oral GC as bridge therapy in the beginning of TNFi therapy, susceptible patients discontinuing the treatment, reactivation of latent infection (e.g., tuberculosis), and the fact that AEs occurring soon after starting a new treatment may be more likely to be reported. In contrast, Kroesen *et al.* (2003) did not find a time-dependency of infections.

Infections were reported in approximately equal proportions of patients using various biological agents (IFX 4.8%, ETA 5.2%, ADA 4.3%, and anakinra 3.1%, p=0.64). The most frequently reported infections were upper airway infections (35 patients), pneumonia (23 patients), sinusitis (20 patients), urinary tract infection (18 patients), erysipelas (12 patients), wound infection or infected eczema (12 patients), bronchitis (11 patients), and herpes zoster (11 patients). The serious infections are reviewed in the SAE section. Infections led to discontinuation of the biological agent in 55 patients (1.7% of the total cohort).

Dermatological problems (II, V)

Various eczemas were reported in 117 patients. This corresponded to 3.7% of the total cohort; drug-specific percentages were 4.2% for IFX, 2.4% for ETA, 2.5% for ADA, and 3.1% for anakinra. The eczemas had various manifestations with regard to localization, description, and type; among these, urticaria occurred in 16 patients, and pustulosis palmoplantaris or psoriasis breakout or worsening in six. The mean time to occurrence of eczema was 8.0 months (median 3.8 months, range 0 to 53 months). Eczemas were among the most common sole or co-existing reasons for discontinuation of the biological agent (n=77, corresponding to 2.4% of the total cohort, with no statistically significant differences between the agents).

Other skin or mucosal AEs included injection-site reactions in 26 patients, pruritus in 16, and xerosis in 12. Injection-site reactions led to discontinuation of the drug in only 18 patients (0.6% of the total cohort), with drug-specific proportions of 0% for IFX, 0.4% for ETA, 0.7% for ADA, and 2.0% for anakinra ($p<0.05$).

In a cross-sectional study, TNFi therapy was not associated with an increased prevalence of cutaneous infections, skin tumors, psoriasis, or atopic dermatitis, compared with conventionally treated patients (Davaine *et al.*, 2008). However, the number of patients in the study was relatively small (59 of 187 patients received TNFi therapy), and the patients were not followed from the start of the treatment. It is therefore possible that they were mostly drug continuers with no dermatological problems attributable to the treatment. In the present study, the reported dermatological problems were clustered to the first months of

TNFi or anakinra treatment, which may point to a causal relationship between the drug and the event. However, it is also possible that events occurring early after the patient has started treatment with a new drug are reported more frequently.

Infusion or allergic reactions (II, V)

Infusion or allergic reactions were reported in 87 patients, which corresponded to 2.8% of the total cohort. The mean time to the occurrence of the infusion or allergic reaction was 4.9 months (median 2.3 months, range 0 to 35 months). Infusion or allergic reactions occurred more frequently in patients using IFX (5.1%) than in patients using ETA (1.3%), ADA (0.7%) or anakinra (1.0%) ($p<0.001$). They were among the most common reasons for discontinuation of the biological agent (n=69, corresponding to 2.2% of the total cohort, with drug-specific proportions of 3.9% for IFX, 0.9% for ETA, 0.7% for ADA, and 1.0% for anakinra; $p<0.001$).

Other frequently reported adverse events (II, V)

Various general symptoms (e.g., headache, nausea, tiredness, vertigo, malaise) and elevated aminotransferases were also among the most commonly reported AEs. Aminotransferases were elevated above the upper limit of normal in 23 patients, of whom 19 used co-therapies which may have contributed. (The median alanine aminotransferase (ALT) value among the patients with elevated aminotransferases was 131 units/l; range 78 to 600 units/l). Other laboratory abnormalities included cytopenia in 13 patients and development of autoantibodies in seven.

Comparisons of adverse event rates (V)

The risk of infections appeared to be somewhat increased among RA patients, compared with other rheumatological diagnoses (Table 16). Higher age and longer treatment duration were also associated with an increased risk of infection. Notably, observational data indicate that, while increasing age may increase the risk of serious infection, TNFi therapy does not appear to increase the risk further (Galloway *et al.*, 2011).

Table 16. Comparison of diagnosis (RA *vs.* other rheumatological diagnosis), sex, use of oral GC (at the time of the reported AE, or ever exposed during the follow-up), baseline age, and follow-up time in the register, in patients with or without reported infection, eczema, or infusion or allergic reaction. The total cohort of 3145 patients is included in the analysis. Statistically significant differences are bolded.

	Infection (n=194)		**Eczemas (n=117)**		**Infusion/allergic reactions (n=87)**	
	Univariate OR (p-value)	Adjusted OR (p-value)	Univariate OR (p-value)	Adjusted OR (p-value)	Univariate OR (p-value)	Adjusted OR (p-value)
Dg, RA vs. other	**1.9 (<0.001)**	**1.6 (<0.05)**	**1.7 (<0.01)**	1.6 (0.05)	**2.0 (0.005)**	1.7 (0.06)
Sex, woman vs. man	**1.6 (<0.01)**	1.3 (0.10)	**1.8 (0.005)**	**1.7 (<0.05)**	**2.3 (<0.005)**	**2.0 (<0.05)**
Oral GC, yes vs. no	**0.7 (0.01)**	**0.4 (<0.001)**	**0.6 (<0.05)**	**0.3 (<0.001)**	1.2 (0.53)	0.8 (0.40)
Age at baseline (years)	**1.02 (0.001)**	**1.02 (<0.005)**	1.01 (0.13)	1.01 (0.25)	1.01 (0.31)	1.00 (0.76)
Follow-up time (years)	**1.4 (<0.001)**	**1.4 (<0.001)**	**1.4 (<0.001)**	**1.4 (<0.001)**	1.1 (0.13)	1.1 (0.24)

Dg=diagnosis; OR=odds ratio

Contrary to what would be expected, concomitant low-dose oral GC was not associated with an increased risk of infections in the present study; actually, the odds ratios indicated a decreased risk. GC usage was reported with 97% completeness in ROB-FIN. However, it is possible that the observation of a decreased risk is affected by selection bias. Low-dose oral GC is commonly used as a component in the treatment of RA in Finland (Pincus, 2013). Oral GC treatment may not have been started or may have been discontinued prior to biological treatment in patients susceptible to infections. Interestingly, Smitten *et al.* (2008), using the U.S. based PharMetrics integrated claims database, found oral GC use to increase the risk of hospitalized infection in a dose related manner (RR 1.3 with ≤5 mg/day, and up to RR 3.0 with >10 mg/day), while bDMARD use increased the risk only slightly (RR 1.2). Moreover, in that study, MTX and HCQ use were associated with a decreased risk of hospitalized infection (RR 0.8 and 0.7, respectively); this was thought to be due to a similar type of selection bias that may be relevant to the present observation as well.

Eczemas were reported most frequently among RA patients, women, and patients with longer follow-up (Table 16). Oral GC use appeared to be associated with a decreased risk.

Infusion and allergic reactions appeared to be more common among women than among men. Low-dose oral GC use, age, and follow-up time were not associated with the risk of infusion and allergic reactions in the present study. RA diagnosis was not a statistically significant predictor in the analysis adjusting for the other variables.

The finding that women tended to be more susceptible to various AEs than men is in accordance with other studies of sex differences in AEs, which indicate that, in general, women experience more AEs than men, and that these events tend to be of a more serious nature (Soldin *et al.*, 2011).

The number of concomitant cDMARDs used was higher among RA patients than among patients with other rheumatological diagnoses in the whole cohort of registered patients (mean for the maximum number during the follow-up 1.7 *vs.* 1.4, respectively, $p<0.001$).

However, the number of concomitant cDMARDs did not yield statistically significant univariate nor adjusted odds ratios among patients with reported infection, eczema, or infusion or allergic reaction (data not shown).

8.3.2 Serious adverse events (II, V)

Serious, life-threatening, or fatal SAEs (excluding malignancies, which are reviewed separately) were reported in 98 patients, i.e., 3.1% of the total cohort. Compared with the ROB-FIN register, the Finnish Medicines Agency (Fimea) received more reports on SAEs (but not AEs in general) in rheumatologic patients using biological agents (Joensuu *et al.*, 2013). This may be due to the complete nationwide coverage of the Fimea database. The SAE may also be diagnosed and reported to Fimea by a non-rheumatologist physician, who may not even be aware of the ROB-FIN register.

SAE infections were reported in 58 patients, corresponding to 1.8% of the total cohort. There were no statistically significant differences in the proportions among patients using various biological agents (IFX 1.7%, ETA 1.3%, ADA 1.3%, and anakinra 1.0%, p=0.82). These rates are similar or somewhat lower than those seen in RCTs or other observational studies, in which up to 6% of IFX, ETA or MTX treated patients had SAE infections during the first six to twelve months of treatment (Maini *et al.*, 1999; Klareskog *et al.*, 2004; Listing *et al.*, 2005). This may be due to some underreporting of events to the ROB-FIN register, which, however, probably occurs more with mild/moderate AEs which may not have been reported to the attending rheumatologist (Gäwert *et al.*, 2011). In accordance with the present study, results from several other observational studies indicate that the risk of serious infection is similar across the individual TNFi agents (IFX, ETA, ADA) (Listing *et al.*, 2005; Dixon *et al.*, 2006; Wolfe *et al.*, 2006; Galloway *et al.*, 2011).

In the present study, 13 cases of septicaemia were reported: urosepsis in five, staphylococcal sepsis in three, and one each of Francisella tularensis, pneumococcal sepsis (pneumonia), streptococcal sepsis (erysipelas), empirical sepsis, and an unspecified septicaemia. Tuberculosis (TB) was reported in ten cases, of which six were pulmonary and six were extrapulmonary TB (in two patients simultaneously). SAE pneumonias were reported in seven patients (fatal in one patient with heart failure, life-threatening in one, and serious in five, in addition to the one that led to septicaemia). Unresolved infections requiring hospitalization were reported in five patients (one life-threatening and four serious). Three further life-threatening infections were reported: one endoprosthetic infection, one listeria meningitis, and one perforation peritonitis in a patient with stoma and diverticulitis. Further serious infections were four each of erysipelas (in addition to the one that led to septicaemia) and septic arthritis; three cases of endoprosthetic infection; two each of septic bursitis and wound infection; and one each of herpes zoster, peritoneal abscess, epiglottitis, an unspecified infection in the ankle, and pyelonephritis (in addition, two cases of pyelonephritis not classified as SAE were reported).

Non-infection SAEs were reported in 40 patients (Table 17). The causal relationship between the bDMARD and the SAE is difficult to determine in this observational setting, as many patients used concomitant cDMARDs, GCs, or NSAIDs, or had comorbidities or medications thereof, that may have contributed. The main cluster of non-infection SAEs comprised infusion or allergic reactions, mainly in patients using IFX.

Table 17. Non-infection SAEs reported to the ROB-FIN register by April 2009. Forty-two non-infection SAEs were reported, concerning 40 of 3145 patients. (V)

Adverse event	Classification	Biological drug	Additional information
Infusion / allergic reactions, n=13	Serious n=11	IFX n=7, ETA n=3, ADA n=1	
	Life-threatening n=2	IFX	One anaphylaxis
Myocardial infarction, n=5	Serious n=2	IFX, ETA	
	Fatal n=3	IFX	One with concurrent pulmonary edema
Cerebral infarction, n=5	Serious	IFX n=1, ETA n=1, ADA n=3	
Pulmonary embolism, n=4	Serious n=2	IFX/ETA, ETA	
	Life-threatening n=1	ADA	
	Fatal n=1	IFX	
Vasculitis, n=3	Serious	ETA n=1, ADA n=2	One Wegener's granulomatosis
Cerebral hemorrhage, n=3	Serious n=1	ADA	
	Fatal n=2	IFX, ETA	
Hemiplegia n=2	Serious	IFX	
Eczema n=1	Serious	IFX	
Iritis n=1	Serious	ETA	
Pancreatitis n=1	Serious	IFX	
Multiple sclerosis n=1	Serious	IFX	
Elevated aminotransferases (ALT) n=1	Serious	IFX	Biopsy showed fatty liver and mild hepatitis
Heart failure n=1	Serious	IFX	Required artificial pacemaker
Unspecified SAE n=1	Serious	IFX	

8.3.3 Cancer (II, V)

Data obtained from the Finnish Cancer Registry (FCR) regarding RA patients registered in ROB-FIN by April 2009 (n=1691) revealed 110 cancer diagnoses during the years 1976 to 2008; an additional ten were reported to ROB-FIN that occurred in non-RA patients or that were not verified by the data extraction from the FCR (Table 18). Of the 110 cancers, 59 were diagnosed before treatment with biological drugs. The remaining 51 cancers were diagnosed during or after biological therapy; this corresponds to 3.0% of the RA patients.

Table 18. Cancers diagnosed in RA patients up to the end of year 2008 in the combined data from ROB-FIN and the Finnish Cancer Registry.

Total number of cancer diagnoses up to the end of 2008 in the combined data from ROB-FIN and the Finnish Cancer Registry: 120	
Cancer during or within 1 year after anti-TNF therapy: 37	Breast: 7 Lymphoid and haematopoietic tissue: 5 Melanoma of the skin: 5 Lung: 3 Brain, CNS: 3 Thyroid gland: 2 Prostate: 2 Rectum, anus: 2 Pharynx: 2 Kidney: 1 Urinary bladder: 1 Pancreas: 1 Uterine: 1 Ovary: 1 Ill-defined or unknown: 1
Cancer diagnosed >1 year after last exposure to anti-TNF drug: 12	Breast: 3 Digestive organs: 2 Female genital organs: 2 Lung: 2 Lymphoid and haematopoietic tissue: 1 Melanoma of the skin: 1 Urinary organs: 1
Cancer in patient on biological therapy but not exposed to anti-TNF drug: 2	Digestive organs: 2
Cancer in non-RA patient or not in Cancer Registry: 10	Brain, CNS: 3 Prostate cancer: 2 Breast: 1 Melanoma of the skin: 1 Urinary organs: 1 Digestive organs: 1 Ill-defined or unknown: 1
Cancer before biological therapy was started: 59	

The median time to the cancer diagnosis in the 37 RA patients who were diagnosed during or within one year after TNFi therapy was 1.5 years (range 0.1 to 6.1 years) after commencement.

For the cancer incidence analyses, 1621 RA patients treated with TNFi agents contributed 5129 person-years under risk during the years 2002 through 2008. The overall incidence rate of cancer did not appear to be increased among RA patients treated with TNFi agents, compared with the Finnish adult population (SIR 1.1, 95% CI 0.8 to 1.5; p=0.67). Site-specific SIR calculations indicated that the rates of skin melanoma and pharyngeal cancer were higher than expected among the RA patients treated with TNFi agents (Table 19). The observed incidence rates of the other cancers did not differ significantly from the expected rates.

Table 19. Standardized incidence rates (SIR) comparing cancer incidences during the years 2002 through 2008 in RA patients diagnosed during or within one year after anti-TNF therapy, with those in the Finnish adult population. SIRs were calculated site-specifically for cancers that were diagnosed in >1 RA patient. Statistically significant SIRs are bolded.

Cancer type	SIR	95% CI
Overall cancer	1.1	0.8 to 1.5
Breast	0.7	0.3 to 1.5
Lymphoid and haematopoietic tissue	2.2	0.7 to 5.2
Melanoma of the skin	**4.5**	**1.5 to 10.5**
Lung	1.3	0.3 to 3.7
Brain, CNS	2.3	0.5 to 6.6
Thyroid gland	3.3	0.4 to 11.9
Prostate	0.6	0.1 to 2.1
Rectum, anus	1.6	0.2 to 5.9
Pharynx	**14.9**	**1.8 to 53.5**

In the present study, the risk estimate for cancer in lymphoid and haematopoietic tissue was similar to the nearly three-fold incidence rate of lymphoma found in other studies comparing TNFi treated RA patients with the general population (Wolfe and Michaud, 2004; Askling *et al.*, 2009). Geborek *et al.* (2005), Setoguchi *et al.* (2006), and Askling *et al.* (2009) found a nonsignificantly increased risk of lymphoma (hematologic) malignancy among TNFi treated RA patients compared with those receiving conventional antirheumatic treatment (possibly affected by channeling bias). Whether TNFi agents as such increase the risk of lymphoma remains elusive.

In a Swedish population-based observational study by Askling *et al.* (2005), the overall risk of solid cancers among TNFi treated RA patients appeared to be similar to that of the Swedish general population (SIR 0.9, 95% CI, 0.7 to 1.2). Also a meta-analysis assessing malignancy risk in association with TNFi treatment, based on registers and prospective observational studies, indicated comparable risks of overall cancer among exposed and non-exposed RA patients (risk estimate 1.0, 95% CI, 0.9 to 1.1) (Mariette *et al.*, 2011). However, the risk of non-melanoma skin cancer appeared to be higher among the TNFi treated patients in the study by Askling *et al.* (2005) (SIR 3.6, 95% CI, 1.8 to 6.5), as well as in the meta-analysis by Mariette *et al.* (2011) (risk estimate 1.5, 95% CI, 1.2 to 1.8); in the meta-analysis, the risk estimate of melanoma was 1.8 (95% CI, 0.9 to 2.7).

TNFi agents have not apparently been associated with pharyngeal cancer previously. In the present study, two cases were found, yielding a high SIR since this form of cancer is quite rare. The cases differed histologically; one was a squamous cell carcinoma, and the other was a lymphoma. Patient-specific information regarding known risk factors for this type of cancers (such as alcohol consumption and smoking) was not available.

In summary, while the risk of overall cancer does not appear to be increased among RA patients within the first few years of TNFi therapy (compared with the general population), some signals of a possible increased risk of certain types of cancer exist. However, being uncommon or rare diseases among persons with a relatively rare exposure (TNFi therapy), these signals are based on modest numbers. Therefore, longer follow-up and larger collaborative studies would be required to obtain more precise estimates (Setoguchi *et al.*, 2006). Comparison to a relevant cDMARD treated cohort could allow a better isolation of

the eventual risk attributable to TNFi therapy. It is also important to note that the results are valid only in the setting from which they are derived. Changes in the selection of patients for TNFi therapy may influence the observed risks (Askling *et al.*, 2005; Askling *et al.*, 2009).

8.4 Cost-effectiveness of infliximab therapy (III)

297 patients fulfilled the selection criteria of Study III (Virkki *et al.*, 2008) at the time of data extraction in January 2007. Their baseline characteristics are presented in Table 20.

Table 20. Baseline characteristics of the Study III cohort.

Age (mean±SD)	51±11 years (range 18 to 78 years)
Sex	Women 69%
Disease duration (median)*	10 years (range 0 to 47 years)
HAQ score (median)	1.250 (range 0.0 to 3.0)
Concomitant oral GC	87%
At least one concomitant cDMARD	96% ▪ methotrexate 66% ▪ hydroxychloroquine 26% ▪ sulfasalazine 18% ▪ leflunomide 14% ▪ azathioprine 8% ▪ sodium aurothiomalate 8% ▪ cyclosporine 7% ▪ podophyllotoxin derivative 7%

*) Calculated from the year of diagnosis

Approximately half of the patients fulfilled the Current Care recommendations for commencement of TNFi therapy. In these patients, the median values of the clinical criteria were: SJC 14, TJC 16, ESR 50 mm/h, and CRP 5.2 mg/dl. In those who did not fulfill the recommendations, the corresponding values were: SJC 7, TJC 6, ESR 22 mm/h and CRP 1.6 mg/dl. Due to the IFX package size of 100 mg/vial, the IFX dose was typically 200 mg (in two-thirds of the patients) or 300 mg (in one-fourth).

At the time of analysis, the patients had been treated with IFX for an average of 21 months (range 1.5 to 78 months). A gain in quality-adjusted life years (QALY gain) occurred in 76% of the patients (n=225); their utility scores improved during IFX treatment. Due to the varying follow-up times, the QALY change was divided by the number of years that the patient had received IFX therapy; each year of IFX therapy led to a mean QALY gain of 0.179, equivalent to 65 days of perfect health (0.179×365). The median utility was 0.446 at baseline, and 0.704 at all subsequent control time-points up to five years.

Around one-third (35%, n=79) of the patients with QALY gain had an incremental cost-effectiveness ratio of ≤40,000 €/QALY gained. The cost per QALY gained (CQG) had a mean and median value of 153,121 € and 51,884 €, respectively. Obviously, some patients with a very high CQG had a major impact on the cost-utility. Their HAQ scores and/or

global VAS fluctuated during the course of the treatment, leading to only a small net gain in QALY (despite improvements in, e.g., joint counts).

Subgroups with CQG ≤40,000 € (Group 1), CQG >40,000 € (Group 2), and no QALY benefit (Group 3) differed significantly with regard to baseline HAQ score and global VAS ($p<0.001$; Table 21). The highest values were seen in Group 1, indicating more severe functional limitation and higher disease activity in this group. Correspondingly, the baseline utility score was significantly lower in this group ($p<0.001$). The largest improvements in HAQ, global VAS and DAS28 score were seen in Group 1. Therefore, in the short- to medium-term, cost-utility was essentially affected by the potential for major improvement in functional ability due to amelioration of disease activity. The response to treatment according to the relative outcome measure ACR50 was also better in Group 1 than in the other subgroups. At three months after commencement of IFX therapy, the ACR50 response rate was 64% in Group 1, 42% in Group 2, and 22% in Group 3 ($p<0.05$). However, the differences in DAS28 remission rates between the groups (46%, 35% and 26%, respectively) were not statistically significant. The effect of prevention of functional decline (as measured by HAQ) due to progressive joint damage would require prolonged follow-up to become evident.

Table 21. Comparison of baseline HAQ score, patient's global assessment (mm VAS), and utility score in patients with CQG ≤40,000 €, CQG >40,000 €, and no QALY benefit (total n=297). Values are means.

	CQG ≤40,000 € (Group 1, n=79)	CQG >40,000 € (Group 2, n=146)	No QALY benefit (Group 3, n=72)
HAQ score	1.73	1.25	1.07
Patient's global (mm VAS)	74	61	48
Utility score	0.38	0.51	0.59

Group comparisons also revealed that Group 1 had the largest proportion of women (85% *vs.* 62% and 65% in the other subgroups, respectively, $p<0.005$). The women had higher baseline HAQ scores than the men (median 1.44 *vs.* 1.00; $p<0.001$); indeed, female sex has been found to be a predictor of disability in RA patients (Scott *et al.*, 2000). The median IFX dose was 200 mg in all groups; however, a relatively small proportion of the patients in Group 1 used doses higher than 200 mg (13% *vs.* 35% and 29%, respectively; $p<0.005$). The dose of IFX may affect the cost-utility; treatment of a "light" patient may inherently be more cost-effective than treatment of a "heavy" patient, owing to the lower dose of IFX.

A somewhat larger proportion of patients with QALYs gained used concomitant MTX (72% and 77% *vs.* 57% for Groups 1, 2, and 3, respectively; $p<0.05$). This indicates that the combination of IFX and MTX may be more cost-effective than treatment with IFX without concomitant MTX. Baseline joint counts, ESR, CRP, age, and disease duration did not differ significantly between the subgroups (SJC54, $p=0.06$; SJC28, $p=0.28$; TJC53, $p=0.05$; TJC28, $p=0.11$; ESR, $p=0.65$; CRP, $p=0.60$; age, $p=0.27$; disease duration, $p=0.80$). The Current Care recommendations for commencement of TNFi therapy were fulfilled in comparable proportions (54%, 46%, and 47%, respectively; $p=0.54$). This might indicate that the trend toward starting TNFi treatment earlier in the disease course and in less severe disease does not substantially affect the cost-effectiveness when only direct medical costs

of the treatment are considered. In fact, HAQ scores, global assessments, utility scores and CQG among patients diagnosed ≤3 years (n=30) *vs.* >3 years before commencement of IFX did not differ statistically significantly (HAQ, p=0.60; patient's global, doctor's global, and pain assessments, p=0.77, p=0.17, and p=0.44, respectively; utility score, p=0.91; CQG, p=1.00). However, the proportion of patients with a HAQ score ≥2, indicating severe functional limitation, was larger in the latter group throughout the follow-up. Some of the patients in the present cohort may have developed permanent joint damage due to longstanding progressive RA before the biological drugs became available. Joint damage has been estimated to account for up to 25% of disability in established RA (Scott *et al.*, 2000). Therefore, it could be supposed that the cost-effectiveness (including averted indirect costs) of TNFi agents is improved in cohorts of patients who have started their treatment when functional disability is more amenable to pharmacological intervention.

In ACR50 responders at three months, the median DAS28 score was 2.3, and the DAS28 remission rate was 65%; in ACR50 non-responders the corresponding values were 4.2 and 13% (p<0.001 for ACR50 responders *vs.* non-responders). Among the ACR50 responders, the CQG was significantly lower compared with that of the non-responders (median 42,960 € *vs*. 62,141 €, respectively; p<0.05). Thus, ACR50 response at three months (the primary outcome measure of the 2003 Current Care recommendations for continuation of a bDMARD) was associated with a significantly higher DAS28 remission rate and a lower CQG than those seen in ACR50 non-responders.

The CQG of TNFi therapy has ranged from <10,000 € to >150,000 € in published studies (Wong *et al.*, 2002; Kobelt *et al.*, 2003; Brennan *et al.*, 2004; Kobelt *et al.*, 2004; Welsing *et al.*, 2004; Kobelt *et al.*, 2005; Brennan *et al.*, 2007). Thus, the costs cover the range from cost-effective to not cost-effective according to conventional thresholds (Wong *et al.*, 2002; Rawlins and Culyer, 2004; Maetzel, 2005; Rawlins *et al.*, 2010). The setting, methodology and assumptions across the studies are not uniform, and comparisons between them may be confounded by, e.g., the method of deriving utility scores and differing comparators, time horizons, discount rates, and attribution of direct and indirect costs. In the present study, which considered only direct drug and administration costs of IFX in an observational cohort, the CQG was similar or slightly higher compared with most of the earlier published cost-utility analyses (CUAs). Inherently, the result is affected by the prevailing treatment practices, including, e.g., the decisions to continue, discontinue or change the treatment. In view of the number of bDMARDs currently available and the common practice of switching between them, long-term studies may need to investigate goal-directed treatment strategies rather than individual drugs. Demonstration of the cost-effectiveness of biological agents in the context of modern treatment approaches and trends will be necessary, as they may have a significant impact on the use of bDMARDs and perhaps also on long-term outcomes (Gómez-Reino *et al.* 2012).

8.5 Outcomes of switching anti-TNF agents (IV)

Of the 1,688 registered patients receiving biological therapy for RA up to April 2009, with a mean follow-up time of 28 months (range, 0 to 105 months), 623 (37%) had switched biological drugs. 479 patients fulfilled the selection criteria of Study IV (Virkki *et al.*, 2011). Of these, 152 switched IFX to ETA; 98 switched IFX to ADA; 102 switched ADA to ETA; 104 switched ETA to ADA; 15 switched ETA to IFX; and eight switched ADA to

IFX. Switching to IFX was relatively scarce, presumably due to the reimbursement system. Therefore, sub-analyses focus on the switches to ETA and ADA.

The characteristics of the cohort were: women 74% (n=355); median age at baseline 52 years (range 18 to 83 years); and disease duration at baseline (calculated from the year of diagnosis) 9 years (range 0 to 48 years). At baseline, 91% used a concomitant cDMARD (56% used MTX), and 88% used oral GC. Values of the ACR core set measures and disease activity are given in Table 22. The mean follow-up time of the first TNFi agent in the present study is 12.9 months (median, 8.8 months; range, 0 to 73 months), and of the second agent, 17.4 months (median, 10.7 months; range, 0 to 63 months).

Table 22. Baseline values of the ACR core set measures and disease activity (DAS28) in the cohort switching an initial TNFi agent to a second one. Values are median (range). A baseline report was available for 377 of the 479 patients included in the study.

SJC	10 (0–44), n=367
TJC	10 (0–53), n=355
Patient's global (mm VAS)	65 (0–100), n=344
Pain (mm VAS)	65 (0–100), n=343
ESR (mm/h)	32 (0–149), n=364
CRP (mg/dl)	2.5 (0–18.9), n=362
HAQ score	1.3 (0.0–3.0), n=341
Doctor's global (mm VAS*)	65 (14–100), n=314
DAS28 score	5.3 (2.1–8.5), n=266

*) Up to year 2004, register forms had a 5-grade Likert scale, which has been converted to 100 mm VAS according to the following: grade 1, 0 mm; grade 2, 25 mm; grade 3, 50 mm; grade 4, 75 mm; grade 5, 100 mm.

Of the 479 switchers, 242 discontinued their first TNFi agent due to lack of effectiveness (LOE) (hereafter referred to as LOE switchers)[5]. Primary LOE (pLOE) was a more common switch reason than secondary LOE (sLOE) in the groups who started biological therapy with ADA or ETA, while primary LOE and secondary LOE was evenly divided within those who started biological therapy with IFX.

Overall, compared to the baseline, the studied outcomes, i.e., SJC, CRP, and DAS28, were lower at the 3 months, best and last observations of both the first and second agents in patients who discontinued the first agent due to LOE ($p<0.001$). The outcomes of the second agent tended to be better than those of the first agent when comparing corresponding observations on the first and second agents, i.e., their 3 months, best and last observations, and, in addition, when comparing the last observation before the switch to the observations after the switch ($p<0.05$ for all comparisons except best SJC on the first agent *vs.* best SJC on the second, $p=0.08$).

Outcomes at three months after the LOE switch are shown in Table 23. In comparing the drug-specific types of switches, the differences in proportions of patients with a clinically significant DAS28 improvement, or in those obtaining an ACR50 response, did not quite

[5] IFX to ETA n=65 (median time to switch 15 months), IFX to ADA n=48 (median time to switch 14 months), ADA to ETA n=54 (median time to switch 6 months), ETA to ADA n=61 (median time to switch 6 months), ETA to IFX n=9, and ADA to IFX n=5

reach statistical significance (p=0.11 and 0.06, respectively). The type of LOE (primary or secondary) did not have a significant effect on the rate of clinically significant DAS28 improvement (p=0.27). However, the type of LOE seemed to affect ACR50 response rates (p<0.001). The odds ratio of ACR50 response in sLOE was 5.5 (p<0.001).

Table 23. Outcomes at three months after the LOE switch: proportions of patients with a clinically significant improvement of the DAS28 score (>1.2 points compared to the last observation before the switch); and ACR50 response rates (compared to the baseline). In the first column, the numbers of patients refer to each corresponding LOE switch subgroup. In the remaining columns, the numbers of patients refer to those with sufficient reported data from the three months visit after the switch.

Drug-specific type of switch	Clinically significant DAS28 improvement	Odds ratio of clinically significant DAS28 improvement	ACR50 response	Odds ratio of ACR50 response
IFX to ETA (n=65)	40% (n=10/25)	3.7 (p=0.06)	24% (n=8/33)	1.3 (p=0.69)
IFX to ADA (n=48)	36% (n=8/22)	3.1 (p=0.10)	50% (n=10/20)	4.0 (p=0.03)
ADA to ETA (n=54)	44% (n=15/34)	4.3 (p=0.02)	19% (n=6/31)	1.0 (p=0.95)
ETA to ADA (n=61)	15% (n=4/26)	Referent	20% (n=6/30)	Referent
Type of LOE				
Primary (n=122)	32% (n=23/71)	Referent	15% (11/75)	Referent
Secondary (n=65)	44% (n=12/27)	1.7 (p=0.27)	49% (19/39)	5.5 (p<0.001)

Disease activity parameters of patients with initial IFX had increased from lower on-treatment values by the last observation prior to the switch, although SJC, CRP, and DAS28 (except DAS28 for IFX to ETA switchers) were still statistically significantly lower than at baseline. For these parameters, the switch to ETA or ADA restored the response initially achieved with IFX (Figure 7). As with patients with initial IFX, disease activity parameters of patients with initial ADA had also increased from lower on-treatment values by the last observation prior to the switch, so that CRP and DAS28 were not anymore statistically significantly different from baseline. The switch to ETA restored and even improved the responses in SJC, CRP, and DAS28 (Figure 7). The disease activity parameters (SJC, CRP, and DAS28) of patients with initial ETA fell significantly from baseline, and were maintained, but not further improved, after switching to ADA (Figure 7).

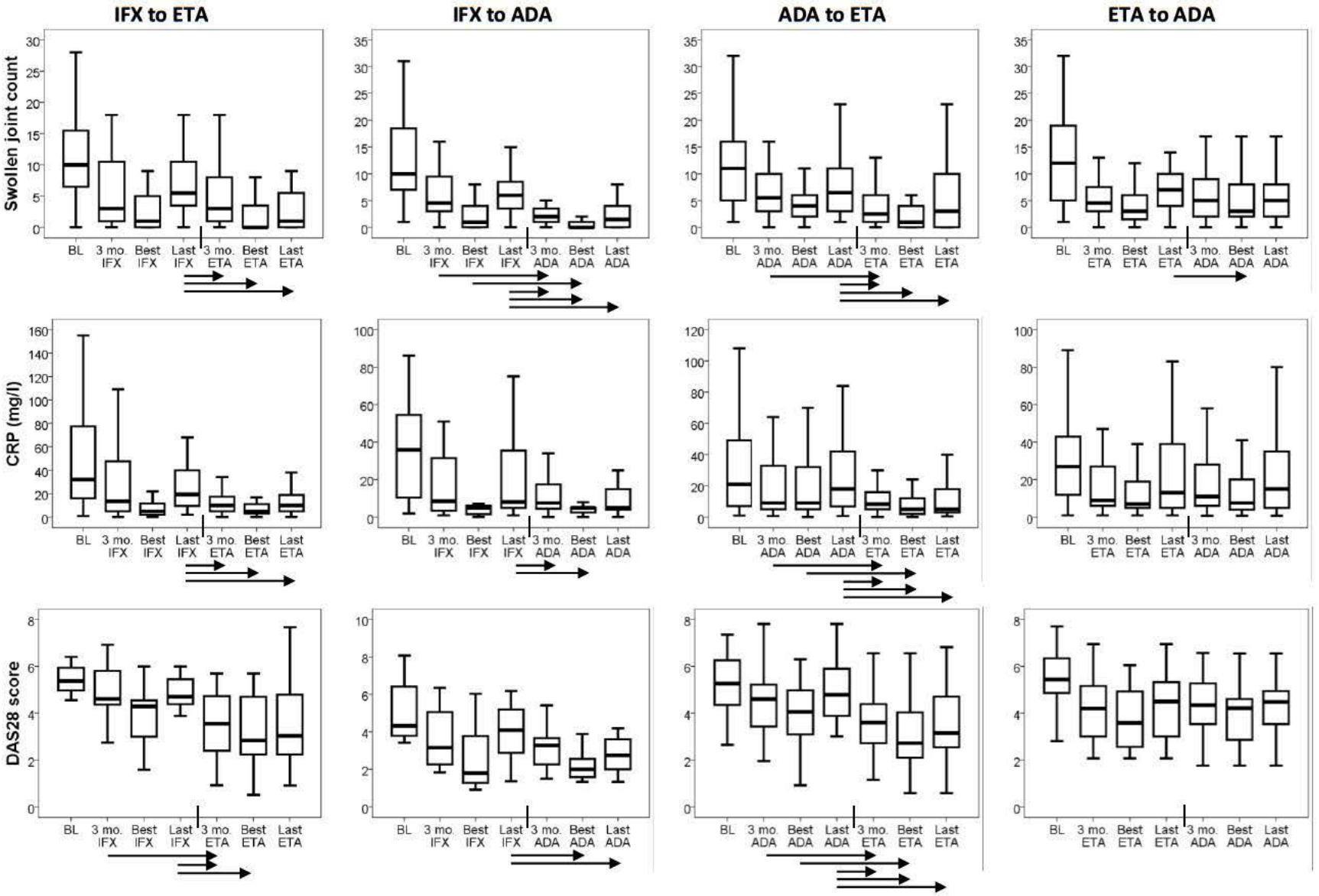
IFX to ETA
IFX to ADA
ADA to ETA
ETA to ADA
Swollen joint count
CRP (mg/l)
DAS28 score
BL
3 mo. IFX
Best IFX
Last IFX
3 mo. ETA
Best ETA
Last ETA
3 mo. ADA
Best ADA
Last ADA

Figure 7. SJC, CRP and DAS28 score of LOE switchers at baseline (BL) before commencement of anti-TNF therapy and at the 3 months, the best and the last observations before and after the switch. LOE switchers with reported BL and at least the 3 months controls of both the first and the second agent are included in the figure. The line transversing the X-axis marks the switch. Y-axes are scaled for each switch type separately. The horizontal line in the box represents the median. The box encloses the interquartile range. The whiskers extend to the minimum and maximum values, excluding outliers and extremes. Arrows indicate statistically significant differences ($p<0.05$) between paired observations (3 months controls, best observations, and last observations, respectively), and between the last observation *vs.* subsequent observations after the switch. The arrow head points to the more beneficial outcome. The number of included patients for IFX to ETA, IFX to ADA, ADA to ETA and ETA to ADA, respectively, are: SJC: 36, 24, 38 and 32; CRP: 36, 24, 34 and 29; DAS28: 11, 12, 24 and 14. The corresponding assessable outcomes of the excluded patients are similar to those of the included patients (data not shown). Outcomes of tender joint counts (TJCs) followed similar patterns as those of the SJCs, but were not as frequently statistically significant. Statistically significant ($p<0.05$) differences in TJCs were found in the following comparisons: in IFX to ETA, and IFX to ADA switchers, the last observation on IFX *vs.* all subsequent observations after the switch (i.e. the 3 months, best and last), and in ADA to ETA switchers, the last observation on ADA *vs.* the best observation after the switch.

Of the total cohort of 242 LOE switchers, 28% (n=67) had discontinued also the second agent due to LOE after a mean follow-up time of 10 months (median 6 months, range 1 to 50 months). Of the 237 patients who had discontinued their first agent due to other (non-LOE) reasons, only 15% (n=35) had discontinued the second agent due to LOE after similar follow-up times ($p<0.001$). Survival rates up to 36 months with the end point being discontinuation of the second agent due to LOE are shown in Figure 8. The rates were lower for patients who had switched due to LOE, than for patients who had switched due to reasons other than LOE (hereafter denoted non-LOE switchers) ($p<0.005$). Notably, the rates were significantly higher for those who had switched due to sLOE than for those who had switched due to pLOE ($p<0.05$). The rates of the pLOE switchers were significantly lower compared with those of the non-LOE switchers ($p<0.001$), while the rates of sLOE switchers did not differ significantly from those of the non-LOE switchers ($p=0.41$).

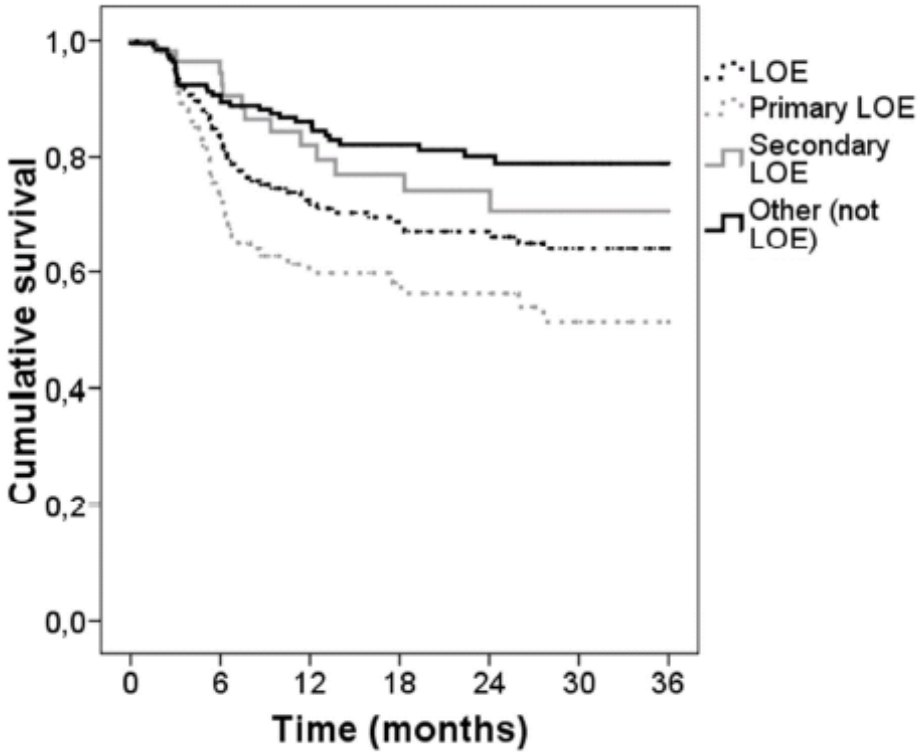

Figure 8. Survival analysis with the end point being discontinuation of the second agent due to LOE. The compared groups are patients who switched their first TNFi agent to another one due to LOE (n=235 assessable out of 242), or due to other, non-LOE reasons (n=227 assessable out of 237). Also shown are the corresponding survival functions of primary LOE (n=115) and secondary LOE switchers (n=63), respectively.

AEs leading to discontinuation of the initial TNFi agent and switch to a subsequent one were mostly infusion reactions, eczema, and local injection site reactions. AEs were the switch reason in 74 patients.[6] Of these, 10% (n=7) discontinued also the second agent due to an AE, after a mean follow-up time of 6 months (median 3 months, range 0.1 to 23 months). Survival analysis with the end point being discontinuation of the second agent due to an AE yielded survival rates at 6, 12, 24, and 36 months of 91%, 91%, 86%, and 86%, respectively, for the AE switchers. These rates did not differ statistically significantly from the corresponding ones of those who switched due to reasons other than AEs. The response achieved with the first agent, which caused AEs, as assessed by SJC, CRP, and DAS28, was maintained, or even improved, with the second agent after the switch.

Other reasons than LOE or AE led to the switch in 163 patients.[7] The reasons for these switches were mostly unspecified and may be diverse, e.g., due to reimbursement reasons (IFX to ETA or ADA), patient preference, and/or unacceptable residual disease activity despite ACR50 response. Overall, the response achieved with the first agent, as assessed by

[6] IFX to ETA, n=25; IFX to ADA, n=10; ADA to ETA, n=23; ETA to ADA, n=13; ETA to IFX, n=2; and ADA to IFX, n=1

[7] IFX to ETA, n=62; IFX to ADA, n=40; ADA to ETA, n=25; ETA to ADA, n=30; ETA to IFX, n=4; and ADA to IFX, n=2

SJC, CRP, and DAS28, was maintained with the second agent after the switch. Subgroup analyses revealed a statistically significant ($p<0.05$) improvement only in the SJC of ETA to ADA switchers, at the 3 months and last observations (means 4.2 and 2.0, respectively, at 3 months; 3.4 and 0.7, respectively, at the last; n=11). Declination occurred in the SJC of IFX to ETA switchers, at the best and last observations (means 0.8 and 2.6, respectively, at the best; 1.9 and 3.5, respectively, at the last; n=27), and also in CRP at the best observations (means 1.3 mg/dl and 1.9 mg/dl, respectively; n=28).

So far, most published studies on the outcomes of switching TNFi agents regard individual switch types, and some pooled data. Most studies lend support for a trial with another TNFi agent in case of LOE or AEs, although results regarding, e.g., outcomes in primary *vs.* secondary LOE and treatment survival and AE rates of the first *vs.* the second TNFi agent are not in complete agreement (Gomez-Reino and Carmona, 2006; Buch *et al.*, 2007a; Hjardem *et al.*, 2007; Hyrich *et al.*, 2007; Conti *et al.*, 2009). However, direct comparisons between studies may be challenging due to the different study contexts and studied outcomes. In the present study, switches were examined from the viewpoints of specific agents and reasons for switching. The results indicate that, for LOE switchers, switching a TNFi agent to another may be of most benefit in secondary LOE (defined as loss of ACR50 response). AEs leading to discontinuation of the initial TNFi agent and subsequent switch to another consisted mostly of infusion or hypersensitivity reactions, and did not predict discontinuation of the second agent due to an AE. However, this result cannot be generalized, since patients may discontinue TNFi therapy altogether after, e.g., a TNFi class-specific and/or severe AE. In general, a similar degree of response achieved with the first agent was maintained with the second agent in patients who switched due to AEs or "other" (not LOE or AE) reasons. Responses could even improve in AE switchers, possibly as a result of better treatment compliance after the switch and resolved AE, although this could not be ascertained in the present study.

The apparent efficaciousness of switching in secondary LOE led us to consider the possible impact of anti-drug antibodies (ADAbs). Up to nearly half of IFX treated patients may develop such Abs during the first year of therapy (Haraoui *et al.*, 2004; Wolbink *et al.*, 2006). Coincidentally, approximately half of IFX treated patients demonstrate secondary LOE during the first year (Buch *et al.*, 2007b). Development of anti-IFX Abs has indeed been associated with decreased serum trough levels of IFX (i.e., serum concentration of IFX just prior to a new infusion) and reduced response to treatment (Bendtzen *et al.*, 2006; Wolbink *et al.*, 2006; Radstake *et al.*, 2009), but does not seem to affect adversely the effectiveness of other TNFi agents (van der Bijl *et al.*, 2008).

Anti-TNF drug switching seemed beneficial also in primary LOE of ADA. Abs against ADA do not seem to form as frequently as those against IFX, but may develop sooner (Wolbink *et al.*, 2006; Bartelds *et al.*, 2007). This may be due to differences in the dose schedules and usage of concomitant MTX. The loading dose regimen of IFX could, perhaps, prevent anti-IFX Ab formation in the beginning of the treatment, since the Ab formation has been found to be inversely related to the IFX dose (Rozin, 2004). Also, MTX may reduce both anti-IFX and anti-ADA Ab formation (Anderson, 2005; Krieckaert *et al.*, 2012). In the present study, MTX use was somewhat more common with IFX than with ADA (63% *vs.* 50%, respectively; $p<0.05$). Formation of neutralizing anti-ETA Abs is uncommon (Anderson, 2005). Switching from ETA to ADA maintained, but did not improve, the responses achieved before the switch. This may lend further support for the benefit of switching in cases where LOE is indeed due to development of neutralizing

ADAbs. However, this cannot be ascertained based on the present study, as data on the eventual presence of such Abs are lacking.

Recently, it has been suggested that assessments of serum drug concentration and ADAb in TNFi non-responders might be useful both clinically and economically in therapeutic decision making (Bendtzen, 2012; Vincent *et al.*, 2013; Bendtzen, 2013) (Table 24). Currently (at the time of study) methods to perform such assessments are not in routine clinical use, and therefore patients with an insufficient response to an initial TNFi agent must often rely on a process of trial and error with subsequent biological drugs based on clinical outcome alone. Immunopharmacological monitoring of individual patients may be justified in that an effective treatment alternative may be found sooner, whereby unnecessary direct and indirect expenses of ineffectual treatment trials may be avoided. Of note, algorithm-based treatment options (based on serum drug and ADAb levels) were shown to be more cost-effective than routine dose escalation of IFX in a randomized controlled trial involving patients with Crohn's disease with secondary IFX treatment failure (Steenholdt *et al.*, 2013).

Table 24. Proposed algorithm to guide treatment decisions based on assessment of serum TNFi drug and ADAb levels in patients with insufficient clinical response to TNFi therapy (due to lack or loss of effectiveness) (Bendtzen, 2012[1]; Vincent *et al.*, 2013[2]).

		Anti-drug antibody	
		Low	**High**
Anti-TNF drug	**Low**	Intensify treatment with the same drug (increased dose or shortened dosing interval)[1,2]	Switch to another TNFi agent[1,2]
	High	Switch to other treatment (biologic with another mechanism of action)[1,2]	Switch to another TNFi agent[2]; Test for neutralizing antibody using cell-based assay / switch to other treatment (biologic with another mechanism of action)[1]

A limitation of the present study is that the results may be affected to some extent by regression to the mean. In most cases, however, TNFi switching was not carried out immediately upon disease activation, as 83% of sLOE switchers had tried some form of optimization of their concomitant medication prior to the switch (e.g., increased dose of IFX, cDMARD, or GC, or addition of a cDMARD or GC). The results of the present study indicate that switching to a second TNFi agent may be beneficial in case of secondary LOE of the first agent or AEs which do not require discontinuation of TNF blocking therapy altogether.

9 LIMITATIONS AND STRENGTHS OF THE STUDIES

The limitations of Studies I to V are the same as those of observational studies in general. Firstly, the patient population is more heterogeneous than those seen in RCTs, since treatment decisions are not restricted by rigorous selection criteria to the same extent. Secondly, the patients are allocated to their respective treatments in a non-randomized fashion, whereby imbalances in factors affecting the outcomes of the treatment may exist. Thirdly, the effects of the intervention (TNFi therapy) cannot be isolated due to the lack of a comparable conventionally treated control group. Fourthly, the reliability of the results is to an extent limited by the incompleteness of the data. Therefore, the results of the studies should be regarded with due caution.

On the other hand, the studies have a strong external validity, at least in the Finnish context, since they reflect the outcomes of TNFi therapy in a large, representative sample of Finnish RA patients using such agents. The studies complement RCT derived data by providing information on effectiveness and safety in a real-life setting.

10 MAIN FINDINGS

10.1 Effectiveness of anti-TNF therapy in the treatment of RA (I, V)

The patients in the study cohort had moderate to severe baseline disease activity and used various concomitant conventional disease modifying antirheumatic drugs (cDMARDs); most had long-standing disease. With roughly two-thirds of the patients achieving an ACR20 response within the first six months of infliximab therapy, the effectiveness was comparable to the efficacy seen in major randomized controlled clinical trials (RCTs) such as the ATTRACT trial (Maini *et al*., 1999). The ACR response rates among patients using various concomitant cDMARD therapies (methotrexate (MTX) with no other cDMARDs; MTX and sulfasalazine with or without other cDMARDs; or cDMARDs other than MTX) were comparable.

Effectiveness (based on ACR response rates) of infliximab, etanercept, and adalimumab was comparable. During a mean follow-up time of 2.3 years, 17% of RA patients discontinued their first biological drug due to lack or loss of effectiveness, and 10% due to adverse events.

10.2 Adverse events of biological drugs in a routine-care setting (II, V)

Adverse events were reported in 17% of all ROB-FIN registered patients during a mean follow-up time of 2.1 years. The most frequent adverse events were various infections (reported in 6.2% of the patients), various dermatological problems (eczemas were reported in 3.7%), and infusion or allergic reactions (reported in 2.8%). Serious, life-threatening, or fatal adverse events (SAEs, excluding malignancies) were reported in 3.1% (fatal 0.2%) of the patients. The main cluster of SAEs was due to infections. Of the various non-infection SAEs the main cluster was due to infusion or allergic reactions.

Data on cancers diagnosed in ROB-FIN registered RA patients was complemented with data from the Finnish Cancer Registry. Fifty-one cancers were diagnosed during or after biological therapy, corresponding to 3.0% of the RA patients. The overall incidence rate of cancer did not appear to be increased among RA patients treated with TNFi agents, compared with the Finnish adult population (SIR 1.1, 95% CI 0.8 to 1.5; p=0.67; the value pertains to RA patients diagnosed with cancer in 2002 through 2008, during or within one year after TNFi therapy). However, site-specific comparisons indicated that the rates of skin melanoma (similarly to other studies) and pharyngeal cancer were higher than expected among the RA patients treated with TNFi agents. However, the assessments are based on modest numbers (five cases of melanoma and two cases of pharyngeal cancer).

10.3 Cost-effectiveness of infliximab therapy (III)

Health-related quality of life, as assessed through a combination of HAQ score and patient's global assessment, improved in 76% of patients upon commencement of infliximab therapy. Of these, roughly one-third had an incremental cost-effectiveness ratio of ≤40,000 €/QALY gained, which can be regarded as cost-effective. This group of patients had higher baseline HAQ scores and global values than the groups with a higher cost per QALY gained, or with no QALY benefit. Therefore, in the short- to medium-term, cost-effectiveness was essentially affected by the potential for major improvement in functional ability due to amelioration of disease activity. Other factors favoring cost-effectiveness included responding to a lower absolute dose of infliximab (e.g., 200 mg as opposed to higher doses), using concomitant MTX, and achieving an ACR50 response.

10.4 Outcomes of switching anti-TNF agents (IV)

Biological drug switches were common, occurring in more than one-third during a mean follow-up of roughly two years. The present study indicates that switching to a second TNFi agent may be beneficial in case of secondary lack of effectiveness (defined here as loss of ACR50 response) of the first TNFi agent or adverse events which do not require discontinuation of TNF blocking therapy altogether. The secondary lack of effectiveness may have been due to development of neutralizing anti-drug antibodies (ADAbs), although this could not be ascertained based on the present study.

11 CONCLUSIONS AND FUTURE VISIONS

This thesis work, based on Finnish nationwide observational data of RA patients treated with biological drugs, indicates that the effectiveness, in terms of relative degrees of improvement (ACR response rates), of TNFi agents in clinical practice is similar to the efficacy in RCTs, even when the biologic was used in combinations with cDMARDs not studied as concomitant therapy in the major RCTs, such as the FIN-RACo combination or even non-MTX cDMARDs. The trend of treating patients with moderate or high disease activity early in the disease course may contribute to the achievement of contemporary treatment aims, most notably remission.

Immunization against chimeric or fully human TNFi agents and production of ADAbs may explain many of the cases of reduced drug response. Development of ADAbs may not be completely preventable, but it might be reduced with the use of sufficiently high doses of TNFi together with concomitant MTX, and possibly by avoiding intermittent treatments. This may require a special emphasis to be placed on adherence to the treatment. In TNFi non-responders, assessment of serum drug concentration and ADAb might be useful both clinically and economically in therapeutic decision making.

Treatment of TNFi refractory RA remains a challenge. The novel biological agents (not targeting TNF) offer alternative treatment modalities, but finding the most effective treatment for individual patients relies to a considerable degree on a sawtooth-like treat-to-target process of trial and error. In view of the high costs of ineffective treatments, both in terms of direct medical costs and possibly indirect costs, it would be important to continue the effort toward personalized medicine. TNFi treatment appears to be cost-effective if current treatment recommendations are followed, involving tight control and sufficient disease control for treatment continuation to be warranted. Nonetheless, in absolute terms, the direct medical costs of TNFi and other biological agents are high. The possible advent of biosimilars in the future might lower the direct costs. Personalized medicine might also bring about cost savings, in addition to individually optimized treatment.

The most common and treatment-limiting AEs comprised of various infections, eczemas and skin reactions, infusion or allergic reactions, various general symptoms, and laboratory abnormalities. The main cluster of SAEs comprised of various infections. Of the non-infection SAEs, the main cluster comprised of infusion or allergic reactions, mainly in patients using infliximab. Compared with the Finnish general population, the overall incidence of cancer did not appear to be increased within the studied cohort, at least not during the first few years of TNFi therapy. However, longer follow-up and larger collaborative studies are required in order to more reliably assess whether the risks of, e.g., lymphoma and skin cancers are increased among TNFi treated RA patients. TNFi therapy appears to be well-tolerated in most patients, but especially in view of the very diverse types of AEs and SAEs which may occur continued vigilance is required. It would be of interest and great practical importance to determine the extent to which information about SAEs reach the attending rheumatologist. In general, collaboration between the valuable clinical registers that exist in Finland would be a feasible way of overcoming some of the data limitations of individual databases, as well as learning more about the short- and long-term health effects of TNFi and other biological agents.

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