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**BIOLOGICAL THERAPIES –  
TREATMENT OUTCOME IN  
RA-PATIENTS: QUALITY OF  
LIFE, HEALTH ECONOMY  
AND PHARMACOTHERAPY**

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**Karolinska  
Institutet**

Stockholm 2010

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ISBN 978-91-7409-773-3

Lycka? Å, det är mycket enkelt! Det är bara god hälsa och dåligt minne!

- Ernest Hemingway



To my Family



## ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory systemic autoimmune disorder characterized by symmetric inflammation of synovial joints, leading to progressive erosion of cartilage and bone. The impact of the disease is wide, not only resulting in decreased quality of life (QoL), but also a loss of productivity and an increase in healthcare costs

The aim of this thesis was to study the impact of treatment with tumour necrosis factor- $\alpha$  inhibitors (TNF-inhibitors) on patients with RA in terms of risk for adverse events, impact on work-force ability and the possibility to predict treatment outcome from early patient reported data. The work is based on three studies using data from the STURE-registry (Paper I, II, III/IV) and ARTIS combined with self-reported data from personal digital assistants (Paper II/IV).

In paper I we investigated the underlying risk factors behind treatment-limiting infusion reactions to infliximab. We found that high inflammatory burden resulting in decreased function, high ESR and subsequently high disease activity together with a high number of previously failed DMARDs increased the risk of experiencing a treatment-limiting infusion reaction. However, daily low-dose prednisone was found to be protective. One important unexplained finding was that the significant decrease in treatment-limiting infusion reactions/year from 1999-2004.

In paper II we investigated the impact of TNF-inhibitor treatment on work-force participation in patients with RA. At baseline patients worked a mean 20 hours/week, in an unadjusted analysis an increase of 4 hours/week was seen after 1 year of treatment followed by a yearly increase of 0.5 hours/week per year on treatment. This was confirmed in a mixed linear regression model, adjusting for confounding factors. Over five year of treatment the expected indirect cost gain corresponded to 40% of the annual anti-TNF drug cost in patients continuing treatment.

In paper III/IV we wanted to explore the early treatment effects of adalimumab. We also wanted to investigate whether early patient-reported data using a personal digital assistant (PDA) could predict treatment outcome at three months and whether joint counts performed by the treating physician could be replaced with patient-reported joint counts. Improvement in pain, hand function, ability to perform basic activities, fatigue and emotional wellbeing all correlated with a favourable treatment outcome at three months. Patient-reported joint status correlated highly with physician reported joint counts both at baseline and at three months. Using a PDA (or other digital instruments) to detect patient-reported data could reveal early trends in treatment outcome and improve standard care. The inclusion of patient-reported data on joint status and other health measurements through digital solutions such as the internet would be both time-saving and give early and accurate information on the fluctuations of the patients individual disease progress without risk of recall bias. If linked to the patient records patient-reported data could give the treating physician a regular update on disease status without time consuming logistics, for both patient and physician, of a scheduled visit/phone consultation.

In summary, registries and observational studies offer an excellent opportunity to study the effects of different treatment strategies in a clinically relevant setting, with full information on and naturalistic managing of concomitant medication etc. The experiences from these studies will lead to a more safe and effective use of the available agents.



## LIST OF PUBLICATIONS

- I. Augustsson J, Eksborg S, Ernestam S, Gullström E, van Vollenhoven R. Low-dose glucocorticoid therapy decreases risk for treatment-limiting infusion reaction to infliximab in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases* 2007;66:1462-1466
- II. Augustsson J, Neovius M, Cullinane-Carli , Eksborg S, van Vollenhoven R. Rheumatoid arthritis (RA) patients treated with TNF-antagonists increase their participation in the work-force - potential for significant long-term indirect cost gains. Data from a population-based registry. *Annals of the Rheumatic Diseases* 2009 May 25. [Epub ahead of print]
- III. Riazoli J, Jacobsson LTH, Nilsson J, Teleman A, Petersson IE, Rantapää-Dahlqvist S, van Vollenhoven RF. Patient-reported outcomes using a hand-held device reveal early trends of improvement in RA patients treated with adalimumab. *Manuscript*
- IV. J. Riazoli, J. Nilsson, A. Teleman, I. F. Petersson, S. Rantapää-Dahlqvist, L. T. H. Jacobsson, R. F. van Vollenhoven. Patient-Recorded Swollen and Tender 28-Joint Counts Accurately Represent RA Disease Activity and Can Be Used To Assess Therapy Responses at the Group Level. *Manuscript*

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## LIST OF ABBREVIATIONS

ACPA	Antibodies to citrullinated protein antigens
ACR	American College of Rheumatology
ARTIS	Anti Rheumatic Treatment in Sweden
CI	Confidence Interval
CRP	C-reactive protein
DAS	Disease activity score
DMARD	Disease-modifying anti rheumatic drug
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
HAQ	Health Assessment Questionnaire disability index
HLA	Human leukocyte antigen
EULAR	European League Against Rheumatism
EQ-5D	EuroQol 5 Dimension
IL	Interleukin
MCP	Metacarpal phalanges
MHC	Major Histocompatibility Complex
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NHS	National Health Service (UK)
NICE	National Institute of Clinical Excellence
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
PIP	Proximal interphalangeal
QALY	Quality adjusted life year
RA	Rheumatoid Arthritis
RCT	Randomised controlled trial
RF	Rheumatoid factor
SD	Standard deviation
SSATG	South Swedish Arthritis Treatment Group
STURE	Stockholm TNF follow-Up Registry
TNF	Tumour necrosis factor

# 1 INTRODUCTION

## 1.1 BACKGROUND

Rheumatoid arthritis (RA) is a chronic inflammatory systemic autoimmune disorder characterized by symmetric inflammation of synovial joints, leading to progressive erosion of cartilage and bone. The prevalence of the disease is approximately 1% of the population, affecting women more often than men. The disease involves the synovial membrane, which becomes inflamed and releases inflammatory cytokines, causing damage to the joint components, cartilage and bone, and thus progressive joint destruction [1]. Indeed, within the first years after the onset of symptoms, there is evidence of joint erosion in most patients [2-4]. Patients with RA can also develop extra-articular manifestations such as vasculitis, nodules, sicca syndrome, or cardiac or lung involvement, particularly those patients who have severe disease [5]. Mortality is increased in a subset of RA patients and this has been related to a high frequency of cardiovascular disease [6]. Thus, the impact of the disease is wide, not only resulting in decreased quality of life (QoL), but also a loss of productivity and an increase in healthcare costs [7]. Tumour necrosis factor- $\alpha$  inhibitors (TNF-inhibitors) have set a new standard in the treatment of RA demonstrating substantial improvement in signs and symptoms, disability, and quality of life, while significantly inhibiting joint damage in early and long-standing RA [8-21]. However careful evaluation at the treatment initiation and long-term surveillance of the patients are necessary. A distinct concern is represented by the high cost of these agents. As the biological therapies that are now available for RA and other diseases are generally needed chronically in these substantial patient populations, an ongoing debate regarding cost-effectiveness will be required with input from clinicians, patients, government and the community.

## 1.2 EPIDEMIOLOGY

### 1.2.1 Incidence

In European and US studies an annual incidence of 0.15-0.46 per 1000 in males and in females of between 0.2-0.88 per 1000 has been reported [22]. Similar numbers were reported by Söderlin et al who found a yearly incidence of 25/100,000 in the adult Swedish population [23]. The incidence rates are generally higher in the USA than in European population based data. Women are affected 2-3 times more often than men, the disease may occur in all age groups, but the average age of disease onset is between 45 and 65 years, in older age groups the incidence appear to decrease [22].

### 1.2.2 Prevalence

The prevalence has generally been estimated at 0.5-1% in western adult populations [24], in Sweden, the prevalence has been estimated to about 0.5% [25]. The prevalence is relatively similar across Europe, North America, Asia and South Africa. However, certain native American Indians, for example Pima Indians, have a higher prevalence [26] and in contrast RA appear to be very rare in rural African black populations [27].

### **1.2.3 Mortality**

Mortality is increased in a subset of RA patients and this has been related to a high frequency of cardiovascular disease [6, 28]. The introduction of a more extensive treatment and reduced disease activity does not appear to have an impact on the increased cardiovascular mortality [29].

## **1.3 ETIOLOGY AND PATHOGENIC FACTORS**

The etiology of RA is still unknown but is believed to be multifactorial, including genetic, environmental and hormonal factors. The rheumatoid synovium is characterized by dense cellular infiltrates, mainly composed of macrophages, T- and B-cells. T-cells play an important role in sustaining the inflammation of RA, with a predominance of T-helper ((Th)1) cells in the synovial infiltrate. However, activated monocyte/macrophage lineage cells also appear to play a major role, as reflected by the presence of excessive quantities of interleukin IL-1, IL-6 and tumor necrosis factor (TNF)- $\alpha$  in the synovium. Biological activities attributed to TNF include induction of proinflammatory cytokines such as IL-1 and IL-6; enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes; stimulation of neutrophil and eosinophil functions; and induction of acute-phase and other liver proteins. Formation and growth of new capillary blood vessels or neoangiogenesis is also observed in the rheumatoid synovium and is considered a key event in the development and persistence of inflammation. Synovial cells and articular chondrocytes release tissue-damaging enzymes, metalloproteinases, which are responsible for the progressive destruction of cartilage and subchondral bone [30-32].

### **1.3.1 Genetics and Environmental factors.**

With the identification of several environmental and genetic risk factors of developing RA an increasing understanding of the pathogenesis is progressing. The shared epitope, a specific sequence of amino acids on the HLA-DRB1 allele is the strongest genetic risk factor of RA [33] and smoking remains the strongest individual environmental risk factors. Smoking is associated with anti-citrullinated protein/peptide antibody (ACPA)-positive RA [34] and a gene-environment interaction between the shared epitope and risk of ACPA-positive RA has been observed in several studies [35-37]. The risk for developing ACPA and RA for an individual who smokes and carries two copies of the shared epitope is 21-fold higher than the risk of a non-smoker who does not carry the shared epitope [38]. Other proposed environmental factors include the role of alcohol consumption, vitamin D intake, intake of protein/red meat, oral contraceptives, birth weight, breast feeding, socioeconomic status and geography [39].

## **1.4 CLINICAL FEATURES**

### **1.4.1 Cardinal symptoms**

The disease onset of RA can vary between acute, sub acute or gradual, the gradual onset being the most common. Several different patterns of disease progression varying from brief and self-limiting to episodic or prolonged and progressive can follow, and long-term radiologic damage has been shown to be the same regardless of the type of

onset [40]. The most common early symptoms of RA with gradual onset consists of a gradual pain and swelling of the small peripheral joints (MCPs, PIPs ankles or wrists) usually in a symmetric pattern accompanied with morning stiffness. Besides pain and stiffness of the joints most RA patients experience fatigue and sometimes depression which can have a larger impact on function and quality of life than the symptoms of the joints [41].

The inflammatory process in the joints causes pain and swelling thus affecting the joint function. Moreover, the release of inflammatory cytokines causes damage to the joint components, cartilage and bone, which leads to a progressive joint destruction [30]. Radiological evidence of joint erosion is present in most RA patients within the first years after onset of symptoms [2-4]. The decreased function of the joints affects the patient in several ways, firstly it's painful and decreases the patients' quality of life [42, 43] and secondly but with time more importantly it affects the patient's ability to work [44] and an increase in healthcare costs with an increased need for joint surgery, rehabilitation etc [45].

## 1.5 CLASSIFICATION CRITERIA

The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis are as follows:

- 1) morning stiffness in and around joints lasting at least 1 hour before maximal improvement
- 2) soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician
- 3) swelling (arthritis) of the proximal inter phalangeal , metacarpophalangeal, or wrist joints
- 4) symmetric swelling (arthritis)
- 5) rheumatoid nodules
- 6) the presence of rheumatoid factor and
- 7) radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints.

Criterion 1 through 4 must have been present for at least 6 weeks. Rheumatoid arthritis is defined by the presence of 4 or more criteria [46].

Although acknowledged in the original paper, the criteria have been criticised for not to perform well in early arthritis. However, the criteria are often used as inclusion criteria in clinical trials in early RA and thus we have very little evidence on treatment outcomes in patients with early arthritis who do not satisfy the criteria set. For these patients an inclusion of MRI [47,48] to detect bone changes before the development of radiologically visible erosions or ultrasound to detect synovial inflammation before clinically detectable swelling [49], might be more suitable criteria. MRI-data have been used in a phase II trial on abatacept in undifferentiated arthritis/very early RA and the results are encouraging [50]. However the study was small and further studies on larger populations is needed for confirmation. The presence of rheumatoid factor have also been questioned since it is not specific for RA but also present in several other conditions associated with chronic inflammation as well as in 5% of the general population[51]. Anti-citrullinated peptide antibodies (ACPA) have a higher specificity

for RA than rheumatoid factor and are also hypothesized to be involved in the pathogenesis of RA thus making it more suitable as a criterion in early RA [52].

## **1.6 DEFINITIONS AND OUTCOME MEASUREMENTS**

Since RA is a disease with multifactorial impact it is not possible to measure disease activity or the effect of treatment with a single instrument. Therefore, several instruments and diagnostic tools are used both to assess inflammatory disease activity, radiological progression and function.

### **1.6.1 Inflammatory disease activity**

The effects on the inflammatory process are measured using the American College of Rheumatology (ACR) core set of outcomes [53], including swollen joint counts (SJs), tender joint counts (TJCs), physician's global assessment by visual analogue scale (VAS), patient's global assessment by VAS, patient's assessment of pain by VAS, health-assessment questionnaire disability index (HAQ), and erythrocyte sedimentation rate (ESR) or c-reactive protein (CRP). Based on these parameters, outcome criteria have been developed, including the ACR response criterion, ACR20, ACR50 and ACR70 [54]. The disease activity index (DAS44) [55] combines SJC, TJC, patient's global assessment and ESR into a single numerical value, and can in turn be used to determine the European League Against Rheumatism (EULAR) response criterion [56]. In clinical practice, the DAS based on 28 joints is usually used: the DAS28 [57].

### **1.6.2 Radiological progression**

Damage progression in RA is usually measured by serial x-ray examination of the hands and feet. Bony erosions and joint-space narrowing at specific joints are scored using one of several systems, usually a modified Sharp method [58]. This score provides a quantitative marker for joint damage, which is necessary in prospective RA studies due to the prohibitively long time required to assess harder damage end points, such as the requirement for joint replacement

### **1.6.3 Function**

The HAQ (health-assessment questionnaire disability index) measures functional capacity, giving information about the individual patient's ability to maintain his or her daily life in a standardized manner [59]. The HAQ has also been shown to be strongly correlated with the patient's perceived QoL [7, 42, 43] and, therefore, preservation of functional status will lead to QoL gains. Preserved function will also decrease the total cost of healthcare for the individual patient. Minimal functional disability (HAQ  $\leq$  0.5) cost about 5000 €, in contrast a patient with severe disease (HAQ  $>$  2) will cost the society 20000 € per year (Swedish data) [60]. Loss of work capacity, most often due to decreased function but in early disease also due to pain and active inflammation, is one of the main contributing factors to the economic burden of RA [7, 42].



## **2 TREATMENT**

The main goals of treatment are to relieve pain, control inflammation and prevent joint destruction. Achieving these goals involves the use of anti-inflammatory agents as well as disease-modifying anti-rheumatic drugs (DMARDs). During the last two decades, there has been a change in the general approach to the treatment of early RA. Prior to the 1980s, the pyramid approach was used in the treatment of RA, beginning with non-steroidal anti-inflammatory drugs (NSAIDs) as a base and then adding medication from different classes and increasing toxicity in a step-wise manner. Today, the pyramid approach has been replaced with a more direct approach that involves the start of treatment with one or even several DMARDs at the time of diagnosis. Once the patient's symptoms have improved and the radiographic damage has ceased to progress, a reduction is made in the dosages and/or number of drugs taken. This paradigm change emerged with the realization that RA appears to be both aggressive and responsive to treatment early in the course of disease and that DMARDs and anti-cytokine agents, such as TNF-inhibitors, control synovitis and slow or even stop radiographic progression [61-64].

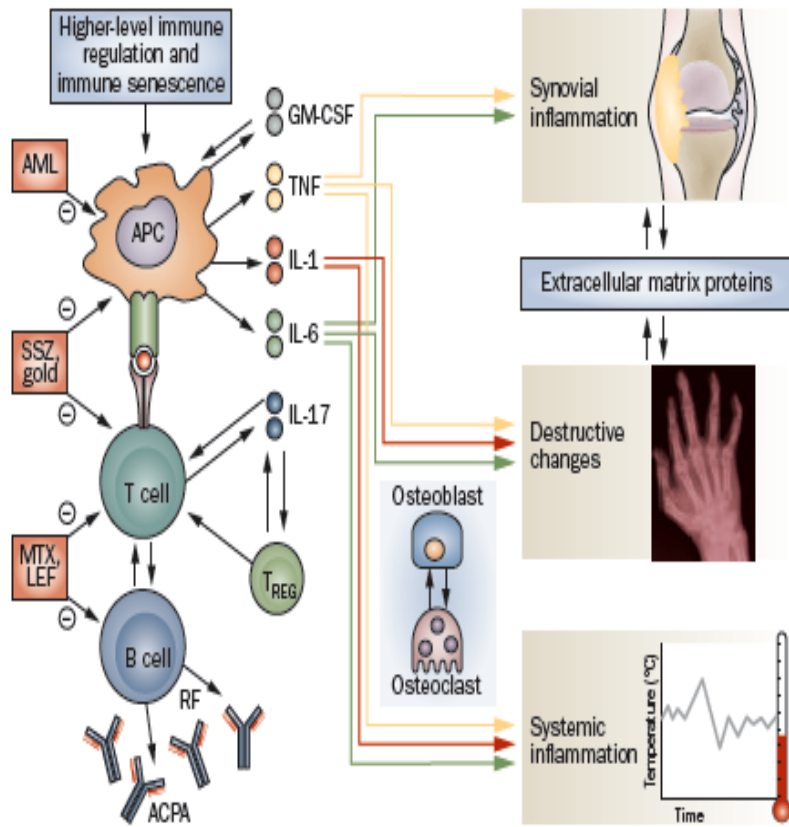


Figure 1. A schematic showing the simplified pathophysiologic pathways in rheumatoid arthritis and their main clinical consequences. Most traditional DMARDs are thought to act broadly against multiple components in this model. Abbreviations: ACPA, anti-citrullinated protein/peptide antibodies; AML, antimalarial drugs; APC, antigen presenting cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; LEF, leflunomide; MTX, methotrexate; RF, rheumatoid arthritis; SSZ, sulfasalazine; TNF, tumor necrosis factor; T<sub>reg</sub>, regulatory cell [65]. Printed with kind permission of Ronald van Vollenhoven

### **3 NEW TREATMENT APPROACHES: BIOLOGICS**

Although DMARDs have resulted in a major improvement in the effective treatment of RA over the past 30 years [66, 67], a sizeable proportion of patients fail to respond, or exhibit a partial response, to these agents [68]. Thus, additional therapeutic options are still needed in many cases. The development of recombinant DNA technology and the possibility of creating monoclonal antibodies have substantially advanced the treatment of human diseases such as RA. These technologies made it possible to clone cytokines and cytokine receptors and to create proteins that specifically counteract the cytokines involved in the inflammation of RA.

Currently approved biologics for the treatment of RA include the TNF inhibitors etanercept [13], infliximab [8], adalimumab [18], golimumab [69] and certolizumab [70], one IL-1 receptor antagonist, anakinra [71], a chimeric monoclonal antibody to the B-cell specific antigen CD20, rituximab [72], a T-cell-activation blocker, abatacept [73] and a monoclonal antibody against IL-6, tocilizumab [74].

Other targets for cytokine-specific therapies include IL-15 [75], IL-18 [76], IL12/23 [77], B-cell directed therapies [78] as well as small molecule compounds such as JAK3- and Syk-inhibitors [79], and these agents are in different stages of development.

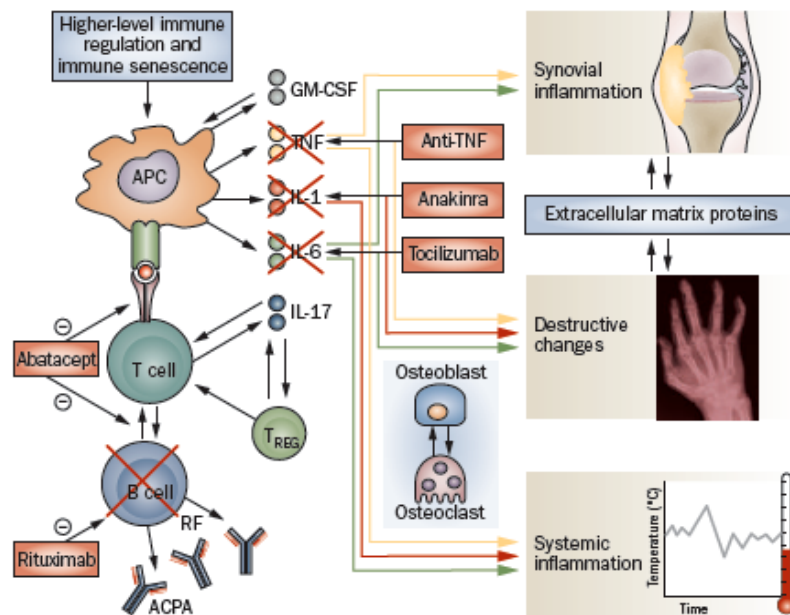


Figure 2. A schematic showing the simplified pathophysiologic pathways in rheumatoid arthritis and their main clinical consequences. Most traditional DMARDs are thought to act broadly against multiple components in this model. Abbreviations: ACPA, anti-citrullinated protein/peptide antibodies; AML, antimalarial drugs; APC, antigen presenting cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; RF, rheumatoid arthritis; SSZ, sulfasalazine; TNF, tumor necrosis factor; Treg, regulatory cell [65]. Printed with kind permission of Ronald van Vollenhoven

### **3.1 3.1 TREATMENT WITH TNF-INHIBITORS**

TNF is a central cytokine in the inflammatory cascade of RA, it is present in high concentrations in the rheumatoid joint and it induces other inflammatory cytokines in the synovial cytokine network [30-32]. This thesis focuses on adalimumab (a human monoclonal antibody), etanercept (a human soluble TNF receptor) and infliximab (a chimeric monoclonal antibody) which were all marketed in Sweden during the time frame of the doctoral studies. A short overview of the characteristics:

#### *3.1.1.1 Adalimumab*

Adalimumab is given as a subcutaneous injection at a dosage of 40 mg every two weeks either as monotherapy or in the combination with MTX. Adalimumab is a fully humanised anti-TNF IgG1 monoclonal antibody that binds to both soluble and membrane bound TNF.

#### *3.1.1.2 Etanercept*

Etanercept is administered as a subcutaneous injection at a dosage of 25 mg twice a week or 50 mg once a week. It is not a monoclonal antibody but is comprised of the extracellular domains of two soluble p75 TNF receptors that are coupled to the Fc portion of IgG1. Etanercept prevents TNF from binding to cell-bound TNF receptors.

#### *3.1.1.3 Infliximab*

Infliximab neutralizes the biological activity of TNF by binding with high affinity to the soluble and transmembrane forms of TNF and thereby inhibiting binding of TNF to its receptors. The recommended dose of infliximab is 3 mg/kg given as an intravenous infusion followed with additional similar doses at week 2 and 6 after the first infusion then every 8 weeks thereafter, infliximab should be combined with methotrexate in the treatment of RA.

### **3.2 CLINICAL EFFICACY**

TNF-inhibitors have been studied in several clinical trials in RA including nearly 6000 patients. Most trials were designed to compare the TNF inhibitor with, or in addition to MTX. The main outcomes in any RA clinical trials are: first, the effects on clinical symptoms and signs, which is effect on the synovial and systemic inflammation; second, effects on radiological progression; and third, effect on function which, as mentioned earlier, has large impact on the quality of life and work ability.

#### **3.2.1 3.1.1 Effect on inflammatory disease activity**

##### *3.2.1.1 Established RA*

Adalimumab, etanercept and infliximab have all been shown to be effective in patients with active RA despite treatment with MTX. In the ARMADA trial patients were randomised to receive 20 mg, 40 mg or 80 mg of adalimumab or placebo every other week while continuing with a stable dose of MTX. After 24 weeks 47.8%, 67.2% and 65.8% of the patients randomised to 20 mg, 40 mg and 80 mg adalimumab achieved an ACR20 response compared to only 14.5% in the placebo plus MTX group ( $p < 0.001$ )

[18]. Patients on a stable dose of MTX were eligible for inclusion in a study comparing MTX plus etanercept or placebo, after 6 months 71 % of the patients on etanercept achieved ACR20 compared to 27% of the patients on placebo ( $p < 0.001$ ) [14]. In the ATTRACT trial, 428 patients treated previously with MTX were randomized to receive placebo or one of 4 dosages/frequencies of infliximab. After 6 months, the proportion of patients achieving the ACR20 response criterion was 53, 50, 58 and 52% of patients receiving 3 mg/kg every 4 or 8 weeks or 10 mg/kg every 4 or 8 weeks respectively, compared with 20% receiving placebo plus MTX ( $p < 0.001$ ) for each of the four infliximab regimens vs. placebo) [8], these results were sustained at 54 weeks of treatment [9].

### 3.2.1.2 Early RA

As radiographic progression can occur early in the disease it is logical to treat proactively with a direct approach in hope of preserving joint function and decrease the risk of co morbidities. The PREMIER study randomised methotrexate naive RA patients with active disease < 3 years duration to 40 mg adalimumab every other week, oral weekly methotrexate plus 40 mg adalimumab every other week or weekly methotrexate. After 1 year 62% of the patients in the combination group achieved ACR50 compared to patients on monotherapy with adalimumab or methotrexate (41% and 46% respectively; both  $p < 0.001$ ). The results were sustained at 2 years with 49% of the patients on adalimumab + methotrexate achieving clinical remission ( $DAS < 2.6$ ) compared to 25% and 27% for adalimumab and methotrexate ( $p < 0.001$  for both) [21]. The effect on clinical remission and radiographic non-progression of the combination of etanercept + methotrexate or methotrexate monotherapy in early RA was studied in the COMET trial. 50 % of the patients in the combination had achieved clinical remission ( $DAS28 < 2.6$ ) at the one year follow-up compared to 28% in the monotherapy group [80]. In the ASPIRE clinical trial, patients with early active RA who had not (yet) been treated with MTX, were randomized to receive MTX plus 3mg/kg infliximab, MTX plus 6mg/kg infliximab or MTX plus placebo and the combination therapy proved to be significantly better also in this patient group) [10]. Sub analysis of the patients with disease duration < 3 years in the ATTRACT-cohort showed similar results [81].

### 3.2.2 Effects on radiological progression

Preserving joint function is one of the key goals in treatment of RA. Methotrexate has been shown to slow the progression of joint destruction [82, 83]. Most studies on radiographic outcome with TNF inhibitors have MTX as an active comparator to monotherapy with a TNF inhibitor or more commonly to a combination of TNF inhibitor + MTX. In the PREMIER study, MTX naive RA patients treated with the combination of adalimumab + MTX had significantly less radiographic progression at both 52 and 104 weeks of treatment than either treatment in monotherapy. Adalimumab in monotherapy also had significantly less radiographic progression than MTX in monotherapy at both time points [21]. Similar favourable results were obtained for the combination of adalimumab and MTX in a study on RA-patients with inadequate response to MTX [84]. The TEMPO trial compared the combination of etanercept and MTX to either therapy alone. The combination was more effective in retardation of

joint damage than etanercept and methotrexate in monotherapy and etanercept in monotherapy was more efficacious than methotrexate in monotherapy [16]. 80% of patients with early aggressive RA showed no progression of joint damage after 52 weeks of combination therapy with etanercept + methotrexate in comparison to 59% of the patients on methotrexate monotherapy [80]. In the ATTRACT study, there was significantly more progression of joint damage from baseline in the group given MTX alone as compared to the groups given infliximab plus MTX at week 54 and 102 [9,85]. Infliximab was found to have a significant benefit on both erosions and on joint space narrowing. Moreover, a significantly higher percentage of patients in the infliximab plus MTX group had an improvement in radiographic scores after 54 weeks of treatment compared to the placebo plus MTX group [9]. The favourable results for the combination were repeated in early RA where two different doses of infliximab (3mg/kg and 6 mg/kg) in combination with MTX were compared to MTX monotherapy. No difference in radiographic progression could be seen between the two doses of IFX but both of them had significantly less progression than MTX monotherapy at the one year follow-up [10].

The favourable radiographic outcome of the combination of a TNF-inhibitor and MTX has been shown to be independent of the clinical outcome measured by ACR20/50/70 or DAS28) [86-90]. However, this may not change physician decision making since a poor clinical response will (and should!) provoke a change in therapy.

### 3.2.3 Effects on function

Functional capacity measured by HAQ gives information on the patient's ability to maintain daily life in a standardized manner [59]. However, as function primarily is restricted by pain and joint swelling in active early RA and to a larger extent by joint damage in established RA a positive treatment outcome is more likely to be seen in early RA than in established RA with irreversible joint destruction [91].

That being said all three TNF inhibitors have shown favourable results in both early and established RA in terms of HAQ. Patients not previously treated with MTX achieved significantly better improvements in HAQ with the combination of adalimumab and MTX than either agent alone. At the two year follow-up 33% in the combination therapy arm had HAQ scores of 0 compared to 19% in each of the monotherapy arms [21]. In established RA the combination of adalimumab (20 mg or 40 mg every other week) and methotrexate resulted in a mean improvement in HAQ score at week 52 of -0.59 and -0.61 respectively compared to -0.25 in with MTX monotherapy ( $p \leq 0.001$  for each comparison) [84]. The combination of etanercept and MTX in early RA led to achievement of HAQ  $\leq 0.5$  in 55% of the patients at week 52 of treatment compared to 39 % of the patients on MTX monotherapy ( $p = 0.0004$ ) [80]. In the TEMPO trial HAQ scores for patients with established RA improved from 1.8 (95%CI 1.7-1.8), 1.7(1.6-1.8) and 1.7(1.7-1.8) to 0.8(0.7-0.9), 1.1(1.0-1.1) and 1.0(1.1-1.1) at the one year follow up for the combination, methotrexate and etanercept treatment arms. The combination was significantly better than either monotherapy ( $p < 0.0001$  for both), there was no difference between the two monotherapy arms) [16]. The trend had also been seen in trials with infliximab. In the ASPIRE trial MTX naive

patients with early RA achieved a significant improvement in HAQ in the combination arms compared to MTX monotherapy with 76% (3mg/kg) and 75.5 % (6mg/kg) achieving an improvement of -0.22 compared to 65.2% in the MTX monotherapy arm ( $p = 0.003$  and  $p = 0.004$  respectively) [10]. Similar results were obtained in the ATTRACT study with patients with established RA, The infliximab plus MTX regimens resulted in significantly greater improvement in HAQ scores ( $P \leq 0.006$ ) at the two year follow-up [85].

### 3.3 STRATEGY TRIALS

Classical randomized double blind studies however well designed and performed cannot answer clinically relevant questions such as: should I treat my patient with treatment X or Y? In an attempt to mimic the clinical reality several strategy trials have been performed.

The BeSt Study, a randomized, single-blinded, 4-arm clinical trial in early RA, showed better clinical and radiographic outcomes with initial combination therapy that included either infliximab or high-dose prednisolone with a rapid taper, when compared to two more traditional DMARD-based treatment strategies (sequentially or as step-up, respectively) in patients with early RA. In the 1-2 year continuation of this trial, a very intriguing observation was made: patients in the group initially treated with MTX + infliximab, who achieved a sustained low level of disease activity ( $DAS44 \leq 2.4$ ), were continued on MTX only (without infliximab) and yet, the vast majority of these patients maintained their low-disease activity state [92]. At the 4 year follow-up 43% of the patients were in remission ( $DAS < 1.6$ ) and 13% were in drug-free remission (14% sequential treatment, 12% step up treatment, 8% initial combination MTX + prednisone, 18% initial combination MTX + infliximab). Clinical and functional improvement was maintained by DAS-driven treatment regardless of therapy. However, initial combination therapy (both prednisone and infliximab) were significantly better in preventing joint damage progression compared with initial monotherapy [93]. Similar observations had previously been reported, albeit based on far fewer patients, by Quinn et al [11]. In the SWEFOT study patients with early RA not achieving  $DAS28 \leq 3.2$  after 3 months of MTX therapy were randomised to combination of MTX with sulfasalazine and hydroxychloroquine or MTX plus infliximab. After one year of combination therapy 25% (32/130) of the patients in the sulfasalazine/ hydroxychloroquine group reached the primary outcome of EULAR good response compared to 39% (50/128) in the infliximab group (risk ratio 1.59[95%CI 1.10 – 2.30],  $p = 0.016$ ) [94]. After 24 months of treatment, the difference in clinical response had decreased and was non significant. However, the combination of infliximab + MTX had a better survival-on-drug (70% vs. 57% respectively,  $p < 0.05$ ) and more importantly the radiographic progression was minimal for 24 month completers in the infliximab group compared to the sulfasalazine/hydroxychloroquine group ( $0.1 \pm 3.19$  vs  $2.77 \pm 7.76$ ,  $p = 0.013$ ) [95]. Another important finding in this open-label study is that even if early remission is important and the combination with a TNF inhibitor is superior to conventional DMARDs, a substantial proportion of patients do well on MTX monotherapy (30% (145/487) at the one year follow-up) [94]. In the GUEPARD study, although an initial favourable response in  $DAS28$  for the initial combination of adalimumab + MTX compared to initial MTX monotherapy was seen



at week 12 no difference in DAS28 or radiographic outcome was seen at the one year follow up regardless of the 3 month delayed initiation of TNF- inhibitor in patients not responding to MTX [96]. Although somewhat different in design, these open-label studies support the “window-of-opportunity” hypothesis in early RA, shown earlier in randomised controlled trials, and provide a new paradigm for treating patients aggressively with close monitoring as soon as the diagnosis is established.

Survival-on-drug has been regarded as a valuable method to study the overall impact of a drug in terms of efficacy and safety. In the ATTRACT study, completion of treatment through week 102 was achieved by 55-68% of the infliximab plus MTX treated patients, compared with 16% of the placebo plus MTX treated patients [85]. At the 4 year follow-up of the ARMADA 62% (162/262) patients had remained in the study and received treatment for a mean of 3.4 years with sustained clinical response and remission. Moreover, reduction of corticosteroid and/or MTX dosages did not adversely affect long term efficacy [97]. In an open extension trial of seven initial trials on etanercept enrolling 581 patients 61.3% (356/581) had 6 years of follow-up and 24.5% (167/581) had seven years of follow-up, the longest individual treatment was 8.2 years. Of the patients with 6 years of follow-up, response rates were ACR20 = 73% and ACR50 = 52% [98].

### **3.4 POST-MARKETING SURVEILLANCE**

#### **3.4.1 Efficacy**

Open-label extension studies and post-marketing studies complements the information from traditional RCTs and provides efficacy and safety information in a more naturalistic setting.

However, in daily clinical practice, patients with RA may differ considerably from those in clinical trials – for example, in their co morbidity and concurrent drug treatment. Population based registers have been developed in several countries to monitor long term efficacy and safety of the biologics. They have provided and will continue to provide information about both efficacy and the true incidence of adverse events [99]. The combined knowledge provided by RCT, open-label extension studies, post-marketing studies and registry data will enhance our understanding of the true benefit of TNF-inhibitors in RA.

The survival-on-drug has been studied in registry studies as well as in RCTs as mentioned above. In a study by Geborek et al, 75% of the patients were still on treatment with infliximab after twenty months, although some had shortened their dose interval or increased dose to sustain symptomatic control [100], and in a Dutch multi-centre registry on biological agents in RA the drug survival rate of infliximab was 66% after one year and approximately 56% after two years [101]. The LOHREN reported a likelihood of continuing therapy with TNF-inhibitors to 78.8% after 12 months, 65.2% after 24 months, and 52.9% after 36 months [102]. In our clinic we have experience of patients with more than seven years of treatment with TNF-inhibitors, as can be seen in paper II.

It has been suggested that the results from RCTs are not achieved in clinical practice due to differences in study design patient inclusion and confounding factors such as

concomitant therapy in clinical practice [103]. In two comparative studies patients from the from the DREAM and RABBIT registry who matched the inclusion criteria in pivotal RCTs (34-79% in DREAM and 21-33% in RABBIT) achieved comparable results as the patients in the original RCTs. Data from these studies indicate that the major reason for differences between observational studies and RCTs is the selection towards a high disease activity in RCTs [104, 105]. Another possibly contributing explanation is the fact that in clinical practice fewer patients used daily prednisone as compared to RCTs where the daily prednisone dose is kept stable [105]. In contrast a glucocorticoid sparing effect has been shown in several observational studies [100,106].

### **3.4.2 Safety & tolerability**

Extensive valuable safety information has been obtained from long term follow-up registries as an addition to the clinical trials that are underpowered to detect rare adverse events. Areas of special consideration for TNF-inhibitors are: infections, lymphoma, congestive heart failure, a lupus-like syndrome, induction of auto-antibodies and infusion reactions.

#### *3.4.2.1 Infections*

As TNF plays an important role in the immune response against infection [107] an increase in infections was expected when treating RA patients with TNF inhibitors. Patients with RA have been shown to be at increased risk of bacterial infections compared with the general population in epidemiological studies, however influences DMARD and/or steroid use are not always considered. For adalimumab, serious infections occurred in the clinical trials at a rate of 5.1 per 100 patient-years (total population of 78522 patient-years), which was comparable to RA populations naive to anti-TNF therapy [108, 109]. In an open-label extension study of etanercept Lebowitz et al reported on a frequency of infections requiring hospitalisation to be 4 per 100 patient-years in the total population (6654 patient-years) [110]. In the two year follow-up of ATTRACT the incidence of serious infections was reported to be 10-13 % in all 5 treatment arms [85]. However, in the ASPIRE trial serious infections were significantly more common in the patients receiving infliximab than in those receiving methotrexate alone ( $p<0.05$  for both infliximab doses) [10]. Safety studies based on national/regional registries indicate a similar incidence of serious infections ranging from 6.4 (German register [111]) to 5.3 (British register [112]) and 5.4 (Swedish register [113]). Overall the infections most frequently reported for all TNF inhibitors were respiratory tract infections and urinary tract infections.

The importance of monitoring patients for signs and symptoms of infections while receiving or after treatment with TNF inhibitors and, in the case of serious infections, (temporary) discontinuation of TNF inhibitor therapy, has been emphasized. A study on the effect of aging on anti-TNF therapy suggested that infections are more commonly observed in elderly patients treated with such agents compared with younger patients [114].

#### 3.4.2.2 Tuberculosis (TB)

TNF plays a major role in host defence against TB, in part through its ability to contain *Mycobacterium tuberculosis* infections by stimulating granuloma formation [107]. Following the introduction of the TNF inhibitors, increasing numbers of TB were reported, for instance by Keane and colleagues, who reviewed 70 cases reported to the US FDA [115] and Gomez-Reino and colleagues, who analyzed data from the Base de Datos de Productos Biologicos de la Sociedad Espanola de Reumatologia (BIOBADASER) database in Spain [116]. The prevalence of TB with TNF-inhibitor use appeared to exceed that of both the general population and that of RA patients. Most of the cases reported were reactivation of latent TB infection [115,116]. These observations have led to widespread implementation of TB screening before initiation of TNF-inhibitors. The screening process should include three parts: thorough TB-related history, skin testing with purified protein derivative (PPD, e.g., tuberculin) and chest x-ray with specific query regarding changes indicative of prior TB. It has been suggested that skin reactivity to PPD may be falsely negative due to the concurrent use of anti-rheumatic drugs such as MTX [117], although experience at our clinic suggests that the skin test may well be positive despite such medication [unpublished observations]. Tuberculin testing may also be less useful in countries where TB vaccination with *Bacillus Calmette- Guérin* (BCG) is common, giving a false positive result. Clearly, patients with active TB should never be treated with anti-TNF agents. Patients who have received full-course therapy for TB in the past may be treated with such agents, but need to be monitored regularly. Patients with (the possibility of) latent TB should be treated for this prior to initiation of anti-TNF. The exact details of such therapy and appropriate time intervals remain a major challenge for the treating physician. Following the implementation of routine screening practices, the number of reported cases of TB has decreased [118]. Moreover, it has been suggested that RA patients are at higher risk of developing TB irrespective of the administration of TNF antagonists [119].

The risk of TB has been proposed to be lower with etanercept than with adalimumab and infliximab. The differential risk is supported by data from the clinical trials with multiple cases of TB in clinical trials and open label extension studies of both adalimumab [21,84,108,120] and infliximab [12,85] but only one case in etanercept trials [121]. A recent study from the French Research Axed on Tolerance of Biotherapies (RATIO) registry also supports the lower risk of TB with etanercept as compared to adalimumab and infliximab [122].

#### 3.4.2.3 Lymphoma & malignancies

In 2002, Brown and colleagues published a case series of 26 lymphoma cases diagnosed during or after treatment with TNF antagonists reported to the US FDA [123]. A study from Sweden also showed that patients treated with anti-TNF therapy had a high relative risk for development of lymphoma compared with healthy controls [124]. However, RA is one of the few clearly identified risk factors for lymphoma, as seen in a number of studies [125,126]. The association is not completely understood, but there are studies that point out that disease severity, for example, high immunological activation, leads to a higher risk of developing lymphoma [127]. Moreover, several older medications used in the treatment of RA have been associated

with an increase in the risk of developing lymphoma (e.g., cyclophosphamide, chlorambucil and azathioprine). Thus, it can be argued that increases in lymphoma risk reflect the fact that the patients receiving these agents have more severe RA and thus are at a higher risk of developing lymphoma to start with. In a Swedish study, Askling and colleagues linked a population- based cohort study of patients with RA to the Swedish Cancer Register [128]. They found that, overall RA patients are at elevated risks for both lymphomas and leukaemia. In contrast, RA patients treated with TNF-antagonists did not have higher lymphoma risks than other RA patients. Although continued vigilance may be appropriate regarding this issue, the conclusion may be that there is no indication that TNF-inhibitors increase the risk for lymphoma over and above the risk conveyed by the disease itself. In a study with similar design comparing RA patients starting anti-TNF therapy to biologic-naïve RA patients and RA patients newly started on DMARDs over a 6 year period no overall elevation of cancer risk and no increase with follow-up time were observed [129].

#### *3.4.2.4 Cardiovascular disease*

TNF has been presumed to play a leading role in the pathogenesis of congestive heart failure (CHF) [131]. This led to several clinical trials with infliximab [131] and etanercept [132] to investigate the effects of TNF inhibition in patients with CHF. These trials were not successful. In trials with etanercept, a lack of efficacy was seen, but in the Anti-TNF Therapy Against Congestive Heart failure (ATTACH) study with infliximab, a concern of worsening of the disease in the treatment arms was raised; CHF hospitalizations and deaths were higher in the high-dose treatment arm and this led to discontinuation of the study in Phase II, a change in product label and a ‘Dear Doctor’ letter warning clinicians of this association. However, post-marketing studies and spontaneous reports to the medical agencies worldwide have not shown that TNF inhibition in RA patients does increase the risk of developing CHF compared with RA patients not treated with TNF-inhibitors [133,134]. Indeed, a study by Jacobsson and colleagues has suggested that the risk of developing cardiovascular disease is decreased in patients treated with TNF-antagonists compared with those patients with RA who are not [135]. This has to be considered against the background of increasing data showing that RA patients have a higher risk of developing cardiovascular disease than the general population [6,136].

#### *3.4.2.5 Demyelinating diseases*

TNF-inhibitors have been associated in rare cases with optic neuritis, seizure and new-onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disorders, including multiple sclerosis (MS) and CNS manifestations of systemic vasculitis. In some cases, it was demonstrated that discontinuation of anti-TNF therapy resulted in complete or partial resolution of the neurological symptoms [137]. The mechanism behind the exacerbation or the de novo onset of symptoms is not known, although several theories are discussed in the literature [138]. However, several studies have pointed out that the numbers reported do not exceed the normal population incidence of MS, and so, although prescribers should use caution in the use of TNF antagonists in patient with pre-existing demyelinating or seizure disease, the

attributable risk for demyelinating disorders with TNF antagonists may be very small indeed [139, 140].

#### 3.4.2.6 *Systemic lupus erythematosus & auto-antibodies*

The incidence of new antinuclear antibody (ANA) positivity was 26–62% in clinical trials with infliximab and the incidence of new dsDNA was 15% [8,9]. Similar figures have been found in post marketing studies [141]. Although the incidence of ANA and dsDNA is quite high, the number of patients who developed drug-induced lupus remains low. Drug-induced lupus is defined as the new occurrence of a lupus-specific feature (e.g., serositis, cytopenia or arthritis) in the context of ANA-positivity and with the resolution of symptoms upon withdrawal of the offending agent. Virtually all of these cases resolved completely after stopping the treatment. Jonsdottir and colleagues reported that the prevalence of anticardiolipin antibodies increased significantly during the first 6 months of treatment with infliximab or etanercept [142]. In that study, patients who developed anticardiolipin antibodies had somewhat worse clinical efficacy of the treatment compared with those who did not.

#### 3.4.2.7 *Immunogenicity*

In early clinical trials of infliximab, formation of human antichimeric antibodies (HACA) was common in patients not receiving concomitant MTX (ranging from 7 to 53%), whereas in patients receiving MTX together with infliximab, the proportion of patients with HACA was significantly lower (0–15%). However, the development of HACA was also decreased in the higher dosage regimens [143]. Patients who were antibody positive were also more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction (see below) than patients who were antibody negative [8,9,143]. Treatment with adalimumab can induce the development of human antihuman antibodies (HAHA) since the unique TNF-binding region as “nonself”. The development of HAHA has been shown to have a negative impact on treatment efficacy [144]. Immunogenicity has been shown as a response to etanercept treatment in RA. However, no correlation has been observed between a positive antibody response and decrease in efficacy [145].

#### 3.4.2.8 *Infusion reactions*

Infusion reactions are a well-described complication of infliximab therapy approximately 20% of infliximab-treated patients in all clinical trials experienced an infusion reaction, with 3% discontinuing the treatment with infliximab due to this reaction [9]. In our unit, several risk factors for infusion reactions have been identified, such as anticardiolipin antibodies [142], high HAQ score at baseline and greater number of DMARDs before treatment with infliximab [146]. In the latter study, we also found that oral low-dose glucocorticoids reduced the risk of treatment-limiting infusion reactions by approximately 50%. In patients with Crohn’s disease, retreatment with infliximab after long intervals may cause a serum sickness-like reaction [147, 148]. It is unclear to what extent this risk is also present in the RA population. In view of the risk for infusion reactions, emergency equipment (such as epinephrine, antihistamines, corticosteroids and artificial airways) should always be available to treat

this rare but sometimes serious side effect. Interestingly, at our centre, the prevalence of serious infusion reactions has decreased dramatically over the years [146].

Injection site reactions have been reported for both adalimumab [149] and etanercept [150], however these injection site reactions tend to be mild and self-limiting.

## 4 HEALTH ECONOMY OF RA

Anti-TNF-treatment has been shown to be highly efficacious in several subgroups of patients, but is also very costly [9,13,18,151]. TNF inhibitors are thus a natural candidate for cost-effectiveness analysis with the aim of finding in which patient subgroups their use provides good value for money. Different perspectives of cost-effectiveness will give different cost estimations. When performed from the perspective of the NHS (payer), as recommended by NICE, indirect costs are disregarded. Reimbursement authorities in other countries, e.g. Sweden, require cost-effectiveness analyses to be performed from the societal perspective, regarding non-medical cost to communities, patients and families and productivity losses as well as the healthcare costs. As the perspective on cost-effectiveness and the resources used for healthcare varies across countries it is challenging to compare cost per patient between countries. However, since the largest contributors to total costs regardless of study/country have been identified as the loss of work-force capacity some cautious assumptions can be made in this aspect.

In a recent cross-sectional study from the south of Sweden physical function measured with HAQ was the main statistical predictor of all types of costs except sick leave which was associated with global health as perceived by the patient [152]. This is in line with other studies where HAQ has been shown to be strongly correlated with work ability [44]. In the study by Jacobsson et al the total cost per patient was 108 370 SEK (adjusted to year 2004 costs), direct costs represented 41% of the total and the use of TNF inhibitors represented 13% of the total costs (or 32% of the direct costs). The indirect costs were dominated by early retirement pensions representing 41% of the total costs [152]. HAQ has been shown to be directly correlated to quality of life [7, 42, 43]. In early RA disease activity and pain have been shown to be important to quality of life independently of HAQ, probably due to the fact that function is dependent on disease activity and pain in early RA to a larger extent than joint destruction [153]. It has also been shown that early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis [154]. The disease leads to early consequences in the context of work capacity in the majority of cases, as exemplified by a Swedish study with 15 years of follow-up reporting work disability rates changing from 28% at study start to 44% at 15 years. HAQ was the only correlating factor that remained significant at all time points during the study period [44].

Direct data on productivity effects of anti-TNF-treatment have henceforth been scarce, and indirect approaches have been used in modelling attempts: evidence of HAQ-reductions while on treatment has been coupled with other data sources showing a relationship between HAQ and productivity [7]. The impact of anti-TNF treatment on work outcomes has been studied RCTs as well as in short term observational studies, but have generated inconclusive results. Yelin et al found significant improvements in hours worked/week over one year in patients treated with etanercept compared to untreated patients [155]. On the contrary, no substantial decrease in cost was found in a recent observational study comparing work disability costs during the first year of

treatment with infliximab to the costs incurred during the year before start of treatment [156]. More recently employment loss was found not to differ between American RA-patients treated with TNF inhibitors compared to matched controls, although it is questionable if the groups were comparable in terms of disease activity. Moreover, in a sub analysis of patients with disease > 11 years a significant benefit was found [157]. Mittendorf et al found sustained work ability over 144 weeks of treatment with adalimumab in an open-label study, but no significant improvement [158]. In a recent RCT treatment with adalimumab was associated with reduced job loss [159]. These results were confirmed in an open-label extension study showing that patients who were working at treatment initiation were able to work 7.3 months longer than the matched control group [160]. One of the problems in the interpretation of these studies is the lack of consensus on how to measure work-force ability, self-reported employability (feeling well enough to work), number of lost workdays, number of hours worked/week are just some of the different outcomes. Moreover, health economic modelling using data from clinical trials gives an overestimation since the design, with no data before baseline, of an RCT is biased towards a greater responsiveness due to selection of patients, the high disease activity at baseline may very well represent a flare in the disease not a chronic state. Secondly the patients in RCT and clinical practice are different in terms of disease activity, co morbidities, concomitant treatment etc [103].

The concept of quality adjusted life years (QALYs) have been developed as a disease-generic outcome measure in economic evaluations, Quality of life (QoL) is combined with life expectancy by weighing life-years with a quality index called utility, defined as the preference that patients have for a given health state. Utility is expressed as value on a scale where 1 = perfect health and 0 = death. The utility can be derived from health state systems which are done for the EQ5D or measured directly using decision analysis techniques [161]. Although mortality is increased in RA the absolute impact in life expectancy is small and therefore QALY gains mainly come from improvements in QoL [162]. The OMERACT Economics workgroup has started an initiative to work towards a consensus on how to calculate QALY in rheumatology. The initiative springs from the fact that different approaches to calculate QALY can lead to different results and thus counteract the original purpose of comparability and transparency between cost-effectiveness ratios of competing interventions [163].

Efforts have been made to model cost-effectiveness of TNF inhibitors from registry data [164,165]. Brennan et al used data from the British Society for Rheumatology Biologics Registry (BSRBR) which at the time had up to 3 years of follow-up on nearly 8000 patients treated with TNF-inhibitors and 900 patients treated with conventional DMARDs. With a life-time perspective the cost per gained QALY by using TNF-inhibitors was estimated at £23 882 for the base case (start of TNF inhibitor therapy after failure on two traditional DMARDs) which is considered cost-effective in the perspective of NICE (only direct costs). The Swedish study by Kobelt et al, included indirect cost. The 10-year costs in the base case (HAQ 1.33, disease duration 12 years, age 55 years) were € 223 000, with a total of 4.4 gained QALYs. Over 5 years, the costs were € 138 000 with a total of 2.5 gained QALYs. HAQ level at treatment start had the highest impact on the result, but underlying disease progression, age, and disease duration was also important. Starting treatment at a lower HAQ level (0.85)



reduces costs by 10% and increased QALYs by 20%. Thus, early treatment leads to reduced costs in patients with rheumatoid arthritis in a Swedish setting. In a recent study on costs of treatment with infliximab in the STURE-registry a cost per QALY of 211 000 SEK was estimated which is well below the established limit of 600 000 SEK/QALY [166].

## 5 AIMS

- to investigate the role of glucocorticoid use and other predictors of infusion reactions in treatment with infliximab
- to determine whether treatment with etanercept, infliximab or adalimumab over up to five years is associated with changes in work force participation in a population-based patient cohort.
  - If an increase in work force participation was present a secondary aim was to explore the economic implications of treatment with TNF-antagonists.
- to describe the early self-reported short-term course of disease in patients with RA starting treatment with adalimumab using a personal digital assistant (PDA), a data-collection system that allows for daily input of self-recorded assessments of the patient's health status.
  - The secondary aim of the study was to evaluate the possibility to predict treatment outcome at three months from diary entries after one week of treatment. In addition, the study aims to explore whether these self-recorded assessments can be useful as a tool in clinical practice
- to determine the utility of patient-derived 28-tender and swollen joint counts using a tablet PC.
  - In the case of high correlations between physician and patient derived joint counts a secondary aim was to explore the possibility to use patient derived data to calculate DAS28 and EULAR response.

## 6 METHODOLOGICAL CONSIDERATIONS

The methods used in this thesis are briefly described below. Detailed information is found in the individual papers.

### 6.1 PATIENTS

All patients in this thesis are registered in the the nation-wide registry for Anti Rheumatic Therapies In Sweden, ARTIS [167].

The patients in paper I and II are collected from the STURE database (Stockholm TNF- $\alpha$  follow-up registry).

The STURE database collects efficacy data, including employment status, and safety data for all patients starting biological treatments at all major hospitals in Stockholm, Sweden. STURE is part of ARTIS. Assessments are done at treatment initiation, and at 3, 6, and 12 months follow-up visits and annually thereafter. These include the ACR core outcomes, i.e. visual analogue scales for global health and for pain, the health assessment questionnaire (HAQ), ESR and CRP, physician's global assessment of disease activity, 28 swollen and tender joint counts and the 28-joint count based disease activity score (DAS28) [55,57]. At each visit, employment status is ascertained in the STURE by a multiple choice question providing the following response alternatives: "I am retired since.....(year).....(month)"; "I work full time .....hours/week"; "I cannot work full time due to my rheumatic disease; I'm currently working ..... hours/week" (follow-up questions on type of sickness benefit/disability pension) or "I cannot state my current work-force ability (unemployed, student, maternity leave)".

In paper I a total of 672 patients treated with infliximab at Karolinska University Hospital at some occasion between 1999 and 2004 were included. Data were obtained from the STURE (Stockholm TNF- $\alpha$  follow-up) registry and by searching patient records when data were missing. Forty-three patients with immediate-type infusion reactions, defined as an anaphylactic reaction and/or urticaria and itching that resulted in discontinuation of infliximab treatment, were compared with the entire cohort and, in a separate analysis, to a nested control group (n=43).

In paper II recruitment from STURE into the study occurred between 1999 and 2007. Therefore the duration of follow-up varied from six months to 8 years. A total of 594 (394 women, 200 men) patients were included. Follow-up after five years of treatment were not analyzed. Only data from the first treatment period for each patient were used since patients could have been treated with several TNF-inhibitors during the study period (1999-2007).

The patients in paper III/IV are also registered in ARTIS, however they were recruited prospectively in a multi-centre observational study including RA patients > 18 years whose physicians had decided to start treatment with adalimumab at the standard dose of 40 mg s.c. every other week.

## **6.2 ETHICS**

Study I was considered a quality assurance project by the regional ethics committee at Karolinska Hospital whom had no ethical considerations regarding the project.

Study II was approved by the regional ethics committee in Stockholm.

Study III/ IV was approved by the regional ethics committee in Stockholm and the Swedish Medical Products Agency.

All patients had given their consent to participate in ARTIS. Patients in study III/IV also gave their written informed consent to participate in the study.

## **6.3 STUDY DESIGN**

### **6.3.1 PAPER I**

Forty-three patients with immediate-type infusion reactions, defined as an anaphylactic reaction and/or urticaria and itching that resulted in discontinuation of infliximab treatment, were compared with the entire cohort (n=672) and, in a separate analysis, to a nested control group (n=43) matched for gender and age. Data were obtained from the STURE (Stockholm TNF-a follow-up) registry and by searching patient records when data were missing.

Comparisons of the following baseline variables were made: HAQ, DAS28, visual analogue scale global and pain, number of swollen joints, number of tender joints, duration of disease at start of treatment, number of failed DMARDs before start of treatment and oral glucocorticoid dose.

### **6.3.2 PAPER II**

Prospectively collected data in the STURE database were analyzed. Patients who were old-age pensioners, on permanent work-disability pension, or those outside the usual work-force (e.g. students, maternity leave etc) or over the age of 55 years at start of treatment were excluded resulting in the cohort of 594 patients. Only data from the first treatment period for each patient were used since patients could have been treated with several TNF-antagonists during the study period (1999-2007).

### **6.3.3 PAPER III/IV**

In this study patients were evaluated by the study physician at the time of inclusion and at the final visit at three months. Swollen and tender joint counts (0-28) were registered by the patients and thereafter by an experienced rheumatology specialist. Health assessment questionnaire disability index (HAQ) and visual analogue scales (VAS) for pain and global health were completed by the patient, and blood samples were taken in accordance with standard practice. All of the data, both physician derived and patient derived, were recorded on a tablet PC. The disease activity score based on a 28-joint count (DAS28) was calculated using both physician and patient derived joint counts.

During the course of the study the patients were requested to answer ten questions as listed below, using a personal digital assistant (PDA). Patients entered data on a daily basis during the week before and the week after start of therapy, and during the last three weeks of the study. During the rest of the study period patients entered data on a weekly basis. At the time of initiation of adalimumab treatment, the patients were evaluated for understanding of and compliance with the self-reporting device (PDA).

#### 6.3.3.1 Primary self-recorded entries

Patients entered data on a daily basis the week before, two weeks after start of therapy and the last three weeks of study, during the rest of the study patients entered data on a weekly basis.

- Global assessment of disease activity  
Considering all the ways your arthritis affects you, place a mark between 0 and 10 on the scale indicating how well you are doing today.  
0 means “My arthritis does not affect at all affect how I am doing” & 10 means “My arthritis does affect maximally how I am doing”
- Global assessment of pain  
How would you generally describe the pain you are experiencing today?  
Place a mark between 0 and 10 on the scale.  
0 means “No pain at all” & 10 means “Maximal pain”
- Assessment of ability to perform basic activities (eat, toilet, dress, bathing)  
How would you describe your own ability to perform basic activities such as eating, bathing, dressing and using the toilet? Place a mark between 0 and 10 on the scale.  
0 means that you are able to do these activities without problems & 10 means that you cannot do these activities at all.
- Assessment of dependency of another person  
How would you describe your need for help from another person to perform basic activities as eating, bathing, dressing and using the toilet?  
Place a mark between 0 and 10 on the scale.  
0 means that you are able to do these activities by yourself & 10 means that you are completely dependent on another person for doing all these activities.
- Assessment of ability to use hands  
How would you generally describe your ability to use your hands today?  
Place a mark between 0 and 10 on the scale.  
0 means “No problems with using my hands” & 10 means “Cannot use my hands at all”
- Assessment of ability to walk  
How would you generally describe your walking ability today?

Place a mark between 0 and 10 on the scale.  
0 means “No problems with walking at all” & 10 means “Cannot walk”

- Global assessment of morning stiffness  
How would you generally describe the morning stiffness you experienced today? Place a mark between 0 and 10 on the scale.  
0 means “No morning stiffness at all” & 10 means “Severe morning stiffness”
- Duration of morning stiffness  
Of what duration was your morning stiffness today? Check the box that applies the best.  
q 15-30 minutes  
q 45-60 minutes  
q 2 hours  
q 3 hours  
q 4 hours
- Global assessment of fatigue  
How would you generally describe the fatigue you are experiencing today? Place a mark between 0 and 10 on the scale.  
0 means “No fatigue at all” & 10 means “Maximal fatigue”
- Global assessment of emotional well-being  
How would you generally describe your emotional well-being today?  
Place a mark between 0 and 10 on the scale.  
0 means “No problems at all emotionally” & 10 means “Severe problems emotionally”

## 6.4 6.4 STATISTICAL ANALYSIS

Statistical analysis was performed using Statview 5.0.1 software (SAS Corp, Cary, NC), SAS (version 9, SAS Institute Inc, Cary, NC) and SPSS (version 15.0). A p-value of <0.05 was considered statistically significant in all studies.

### 6.4.1 PAPER I

Comparisons were by the Fisher’s test for nominal variables, and by Mann–Whitney test and Wilcoxon test for all other variables. Survival on drug without infusion reaction was plotted according to Kaplan–Meier and compared by log rank test (Mantel–Cox). Logistic regression was used to determine odds ratios for continuous variables in the case-control study. The number needed to treat (NNT) [168] was calculated over the study period.

### 6.4.2 PAPER II

Differences between males and females at baseline in age, HAQ, DAS 28, pain VAS and hours worked/week were assessed using independent samples t-tests. Differences

between patient groups defined by drug were investigated using analysis of variance (ANOVA) with Bonferroni's post-hoc test for multiple comparisons. Crude changes in hours worked/week at 6 months, 1, 2, 3, 4 and 5 years were assessed by paired t-tests using complete case analyses. Separate analyses were also performed for patients not discontinuing biologic treatment during follow-up to account for the risk of informative censoring due to drug discontinuation.

To model the trajectory of hours worked/week, a mixed piecewise linear regression model with a random intercept was fitted. This method uses all repeated measurements, taking unevenly spaced measurements and missing data into account and makes it possible to estimate within-subject variations in hours worked/week with great precision as each individual acts as his own control [169]. An attempt to approximate the monetary value of changes in hours worked/week was made by using the mean wage rate in Sweden, retrieved from Statistics Sweden ([www.scb.se](http://www.scb.se)). The productivity gains were estimated by using the most likely conservative assumption that without treatment the hours worked/week would remain unchanged over five years.

#### **6.4.3 PAPER III/IV**

Changes from baseline of the clinical and patient-derived outcomes were assessed by paired t-test. The relationship between the change in PDA measurements after 1 week and changes in DAS28 and HAQ after 3 months were evaluated by Spearman correlation as were the relationship between patient and physician reported measurements; the latter was also evaluated by bivariate regression. Day to day changes in each patient were inspected using individual scatter plots to detect patterns of treatment response or/and problems with compliance.

## 7 RESULTS

### 7.1 TREATMENT-LIMITING INFUSION REACTIONS TO INFLIXIMAB - THE ROLE OF DAILY ORAL GLUCOCORTICOIDS (PAPER I)

Interestingly, the proportion of infusions associated with infusion reactions decreased significantly during the study period, from nine out of 152 patients on infliximab (5.92%) in the year 2000 as compared to five out of 438 patients (1.14%) in 2003 ( $p = 0.0024$ ). The treatment-limiting infusion reactions were recorded at various time points during therapy, slightly more frequent after five or more infusions, most patients identified in our survey experienced several less severe infusion reactions before the discontinuation of treatment. The symptoms were most commonly treated by stopping the infusion and administering intravenous glucocorticoids and/or antihistamines (clemastine). All patients who had experienced an infusion reaction were given prophylactic treatment (intravenous steroids, hydrocortisone and/or antihistamines) before their next infusion 1 h before treatment.

At baseline fifty per cent of the patients in the cohort were treated with daily low-dose glucocorticoids. Of these patients 4.6% (15/326) had an infusion reaction as compared with 8.6% (28/324) of patients without glucocorticoid treatment ( $p = 0.057$ ). In the matched comparison, 15/43 (35%) of the cases were on low-dose glucocorticoids as compared with 27/43 (64%) of the controls ( $p = 0.017$ ). Treatment with oral prednisolone led to a 46.4% risk reduction (95% CI: 3.1 to 74.4%) and interestingly dosage was not a significant predictor.

Patients with infusion reactions had higher HAQ-scores as compared with both the matched control and the cohort: the case group had a median value of 1.75 with an interquartile range of 1.13–2.25 vs. 1.5 (0.63–2.25) for the matched control and 1.38 (0.88–1.88) for the cohort.

In the matched comparison one additional risk factor for severe infusion reactions was identified: the cases had failed to respond to treatment with a greater number of DMARDs than the matched controls (cases  $3.65 \pm 0.32$  (mean  $\pm$  SEM) vs. controls  $2.61 \pm 0.24$  (mean  $\pm$  SEM),  $p = 0.012$ ) before the start of treatment with infliximab

The use of low-dose glucocorticoids was also associated with a significantly lower risk for a treatment-limiting infusion reactions in a Kaplan–Meier analysis ( $p = 0.04$ ).

### 7.2 7.2 WORK FORCE PARTICIPATION IN RA – THE IMPACT OF TNF INHIBITORS (PAPER II)

At baseline patients the included patients worked a mean 20h/week (SD 18). Age, disease duration and pain scores did not differ significantly between the sexes, but females had significantly higher HAQ (0.21;  $p < 0.001$ ) and DAS 28 (0.60;  $p < 0.001$ ) than males. No sex difference was detected in hours worked/week at baseline ( $-2.7$ h;  $p = 0.08$ ).



Patients treated with adalimumab had lower HAQ (adalimumab vs. infliximab -0.23,  $p=0.02$ ; adalimumab vs. etanercept -0.24,  $p=0.01$ ) and higher number of hours worked/week at baseline (adalimumab vs. infliximab 8h,  $p=0.001$ ; adalimumab vs. etanercept 7h,  $p=0.008$ ), most likely reflecting the later market introduction of adalimumab when an intention to treat earlier to prevent irreversible damage had developed. No other between-drug differences were observed during the study period.

Significant improvements in hours worked/week were observed already at six months in an unadjusted analysis: +2.4h (1.3 to 3.5; mean, 95% confidence interval (95%CI)) with further increases compared to baseline at the one-year (+4.0h, 2.4 to 5.6) and two-year follow-up (+6.3h, 4.2 to 8.4). The trajectory appeared to stabilize at the 3 year (+6.3h, 3.6 to 8.9), 4 year (+5.3h, 2.3 to 8.4) and 5 year follow-up (+6.6h, 3.3 to 10.0). When restricting the analysis to only patients who did not discontinue treatment during follow-up, greater increases were observed. The number of hours worked at baseline was similar for patients followed for different durations, and significant increases in productivity were observed irrespective of length of follow-up for the whole sample.

The results were sustained in a mixed piecewise linear regression model, adjusted for age, sex, baseline disease activity, function and pain, were an improvement of +4.2h/week was estimated for the first year followed by an added improvement of +0.5h/week annually during the years thereafter. Restricting analysis to non discontinuers, a greater increase of 5.3h/week was seen during the first year, and 0.9h/week in subsequent years. Adding anti-TNF drug did not improve model fit, and no significant between-drug differences in productivity change could be detected ( $p_{\text{interaction}}=0.79$ ).

We based our economic estimation on the most likely conservative assumption that patients' productivity would not deteriorate from their baseline value over five years without anti-TNF treatment, the productivity gains for society in patients continuing treatment would total €27 000 over five years. This corresponds to approximately 40% of the annual anti-TNF drug cost. When estimating the costs by using the unadjusted data, a similar estimate of €28 000 over five years resulted. These estimates only apply to patients who do not discontinue treatment, a group which may be difficult to identify before treatment initiation.

### **7.3 SELF-REPORTED COURSE-OF-DISEASE IN RA REVEALS EARLY TRENDS OF IMPROVEMENT (PAPER III)**

A total of 47 patients were included and 43 patients completed the study. Significant improvements were seen in DAS28, HAQ, ESR and joint index after three months of treatment with adalimumab. The patient-derived data displayed considerable day-to-day variability in most disease domains during the first week of measurement, the variability decreased after start of treatment. Despite this initial variability, results for 9 of 10 disease-domains demonstrated significant improvements already in the first week of treatment for the total patient group and from pre-treatment to week 12; the exception was "dependence on another person" which remained largely unchanged throughout the study.

One-week improvements in ability to perform basic activities ( $r = 0.40$ ,  $p = 0.01$ ), hand function ( $r = 0.45$ ,  $p = 0.005$ ), morning stiffness ( $r = 0.32$ ,  $p = 0.04$ ), fatigue ( $r = 0.32$ ,  $p = 0.04$ ) and emotional well-being all, albeit some of them only weakly, correlated with the 3-month improvements in DAS28 whereas one-week improvements in global assessment of disease activity, pain, basic activities, hand function, morning stiffness, and emotional well-being were all correlated ( $r = 0.39$ ,  $r = 0.43$ ,  $r = 0.53$ ,  $r = 0.47$ ,  $r = 0.53$ ,  $r = 0.53$   $p < 0.05$  for all) with 3-month improvement in HAQ.

The patients had no major problem using the PDA or completing the questionnaire, although some data were missing due to technical problems in the transferring process. The patients' compliance with the protocol varied considerably, some patients answering more often than requested and other less frequently. In general the answering frequency tended to decline with time.

#### **7.4 PATIENT REPORTED JOINT COUNTS – ACCURACY AND CORRELATION WITH PHYSICIAN REPORTED JOINT COUNTS (PAPER IV)**

47 patients were included prior to initiation of adalimumab therapy and assessed at baseline and after 3 months. The correlations between SJC/TJC derived by physician and by patient at baseline were excellent ( $r = 0.75$  and  $0.87$ , respectively  $p < 0.001$ ). After 3 months, the correlations were less strong for swollen joints but remained excellent for tender joints ( $0.58$  and  $0.87$  respectively  $p < 0.001$ ). The lower correlation for swollen joints was more pronounced for patients with early RA (disease duration  $\leq 2$  years,  $r = 0.51$ ,  $p = 0.2$ )

When using the patient-derived SJC/TJC for calculation of the DAS28 (DAS28-PAT), similar values were obtained, and correlations between DAS28 and DAS28-PAT were excellent ( $r = 0.91$  at baseline,  $r = 0.90$  at 3 months). Patient and physician derived joint counts showed similar correlations with DAS28 and patDAS28 as well as with physician global VAS, acute phase reactants and HAQ.

According to the EULAR-criterion the percentage of responders at the group level was nearly identical. However, there was some disagreement on the individual level when DAS28 and DAS28-PAT were used to determine response to therapy. Patients who differed in EULAR response when using the patDAS28 had a higher HAQ score at baseline (mean difference  $0.455$  (95% CI  $0.08$  to  $0.8$ ),  $p < 0.02$ ) but there were no differences in disease duration or age indicating a more severe disease development.

## 8 PRELIMINARY RESULTS

There is a growing proportion of patients with longstanding response to TNF-inhibitors such as infliximab. There are indications from conceptual studies such as the BeSt and the Quinn study that a subpopulation of patients treated with TNF-inhibitors early in the disease can achieve prolonged remission [11,92]. However, the fact is that in clinical practise the large majority of patients treatment with TNF-inhibitors has been initiated in a later phase of the disease. Furthermore, for a large proportion of the patients clinical experience does not support that achieved remission can be maintained without prolonged maintenance treatment with TNF-inhibitors. Today there is a general demand to optimize medical use, and a dose reduction strategy therefore needs to be explored in the average RA patient population on biological treatment.

The aim of this multi-centre open-label study was to perform a pre-study in the format of a patient-questionnaire combined with data from the Swedish Rheumatology Register (SRR) and the South Swedish Arthritis Treatment Group (SSATG) [167]. Thereby exploring patients able to meet the inclusion/exclusion criteria of a dose decrease study, both in terms of number of patients and need of dose adjustment in clinical practice. A secondary objective was to describe patients being on maintenance therapy with infliximab since at least 12 months and thus, characterizing the national patient population on maintenance treatment with infliximab in terms of number of patients with low disease activity, dose and experienced dose interval. Patients who met the inclusion criteria received oral and written information about the study during a pre-planned infliximab infusion visit and upon consent they also received two questionnaires for completion (EQ5D and a questionnaire on their experience of treatment with infliximab). Clinical data from start of treatment and the two preceding visits was obtained from the SRR and the SSATG.

363 patients participated in this non-interventional study, 70% were women, mean age 61 years (range: 23-89) and the mean disease duration at start of treatment with infliximab was 16.5 years (range: 3-61). Disease activity parameters as DAS28, HAQ, CRP and ESR all improved significantly from start of treatment to the pre-planned visit. 213 patients were assessed as having a low disease activity (DAS28<3.2) at the pre-planned visit, however, 35.7% of the patients considered their disease activity as moderately active. The majority of these patients had current dosing interval of 8 weeks, only 12.2% had a dose interval > 8 weeks. Furthermore, 74.9% of the 363 patients experienced an increase in disease symptoms when the up-coming infliximab treatment was approaching. In contrast, a majority of the patients, regardless of current disease activity, were positive to participate in a future dose reduction study.

In the light of these results it may be difficult to start a dose reduction study based on data from the registries. However, in the individual patient it may be an attractive option to try dose reduction with close monitoring if the patient has reached a stable level of low disease activity/remission.

## 9 DISCUSSION

### 9.1 PAPER I

This retrospective study of a large patient cohort provides important information about the true incidence of treatment-limiting infusion reactions and individual risk factors at baseline. We demonstrate a clear protective effect of daily low-dose oral prednisolone which indicates a reduction in the risk for an infusion reaction by about half. The NNT for a 5-year period to prevent a treatment-limiting infusion reaction was calculated as 25 for low-dose glucocorticoid treatment, which is on the same level as the summarized NNT of 26 for ramipril in the HOPE study [170]. Patients with concurrent prednisolone had a significantly lower risk of experiencing a treatment-limiting infusion reaction.

In the matched comparison, there was a clear statistical difference in glucocorticoid use between the two groups, which further emphasizes that glucocorticoids have a protective function. However, difference in glucocorticoid use did not affect the treatment duration within the case group itself, indicating that several risk factors interact. Hence, even though low-dose glucocorticoid use has a protective effect against treatment-limiting infusion reactions to infliximab, it does not affect the timing of the infusion reaction. Taken together, our results show that low-dose glucocorticoids have several advantages for patients treated with infliximab. Many physicians tend to decrease or stop treatment with glucocorticoids, due to a fear of long-term side effects, when the patient receives a positive response to DMARD treatment. However, low-dose prednisolone has been shown to retard radiographic progression in patients with early RA, albeit with no significant difference in bone mineral density between the prednisolone and no-prednisolone group over the 2-year study period [171].

The prophylactic effect of betamethasone given just prior to the infusion with infliximab was studied in a prospective manner by Sany et al [172]. In that study, the occurrence of infusion reactions was lower in the placebo group, suggesting an increased risk with corticosteroid pre-treatment, most likely explained by infusion reactions caused by the betamethasone itself. The use of oral steroids did not significantly affect the incidence of infusion reactions (14.3% with and 10.3% without oral corticosteroids, respectively,  $p=0.28$ ). However, this comparison did not correct for study treatment (betamethasone vs. placebo), which did show a difference in use of oral corticosteroids between the placebo (84.7%) and betamethasone (77.1%) group. Thus, it appears that their results could well be consistent with ours. In a study by Wasserman et al, pre-treatment with the antihistamine diphenhydramine did not reduce the frequency of infusion reactions. In this study, a rather wide definition of infusion reactions was used, and the conclusions might be biased by the known side effects of diphenhydramine [173].

The formation of anti-infliximab antibodies, also known as human antichimeric antibodies, is a possible risk-factor for the development of infusion reactions [143,174-176]. A retrospective study by Haraoui et al found that RA patients who developed anti-infliximab antibodies were about 10 years younger and were taking about half the mean dose of prednisone [177]. In a previous study at our centre, it was found that the presence of anticardiolipin (ACL) antibodies in patients treated with infliximab was a

risk factor for treatment-limiting infusion reactions. Seventeen per cent of the ACL-positive patients experienced such a reaction, compared with 5% of the patients in the whole registry [142]. A higher HAQ score and a higher number of previously failed DMARDs were also predictors of treatment-limiting infusion reactions in this study. It is possible that the patients who experience a treatment-limiting infusion reaction have suffered a higher inflammatory burden and therefore may be more prone to adverse events by various pharmacological agents, or that the chronic immunological activity itself may predispose to immunological adverse events.

One important unexplained finding in this study was the sharply decreasing number of treatment limiting infusion reactions in our cohort. Several explanations could be considered. First, increased experience among physicians choosing the right pharmacological treatment for each patient. Second, the staff at the day care ward now has several years of experience and has learned to recognize the early signs of an infusion reaction, thus lowering the infusion rate before the reactions develop into something that might lead to discontinuation of treatment. Third, subtle changes in the manufacturing process of the drug may decrease the risk of immunological reactions [178] Our first assumption was that there could be an explanation in the fact that during the first years with TNF-inhibitors, there was a positive selection of patients with high disease activity, and this patient group could be more prone to have an adverse reaction. This seems not to be the case in our cohort, since the median DAS28-scores are on the same level when making a yearly comparison over the study period (not shown). Similar results have been shown for etanercept by Feltelius et al [179]

## 9.2 PAPER II

In this observational study we investigated the development of hours worked/week in RA patients treated for up to five years with TNF-antagonists. At baseline the average patient worked half-time, but during the first year of treatment this was increased by approximately four hours. After the first year smaller annual improvements occurred. The shape of the trajectory was similar to the development in measures of disease activity, physical function and pain, although these measures had a more rapid improvement and had reached a more pronounced plateau at one year. Assuming that the patients' work ability had remained unchanged over five years without biologic treatment, the indirect cost gains from improved work ability in continuers would offset approximately 40% of the drug cost.

The results from the current study are congruent with some previous studies on effects on work ability of anti-TNF-treatment. Yelin et al found significant improvements in hours worked/week over one year in patients treated with etanercept compared to untreated patients and Allaire et al found a significant benefit in the subgroup with a disease duration <11years [155,157]. Recently a study on certolizumab pegol (CZP), the combination of CZP plus MTX showed significant improvements in productivity both outside and within the home and resulted in more participation in social activities compared with placebo plus MTX [180]. The results do, however, conflict with the findings of Mittendorf et al, who could not detect any improvements in hours worked/week over three years of follow-up, although work ability did not deteriorate either, and Laas et al who found no substantial decrease in work-disability costs during

the first year of treatment with infliximab [156,158]. The sources of these discrepancies may be different length of follow-up, differences in disease severity in the samples investigated, and differences in the labour market in the respective countries. Furthermore, the lack of or specific choice of control group may also contribute.

Anti-TNF-treatment led to large and sustained improvements in both disease activity and disease function over up to five years in this study, which was paralleled by improvements in work ability. The small increases in work ability observed beyond year one, at which time the clinical effect of TNF-antagonists stabilized may reflect inertia in the labour market or at the patients' work place. However, these small improvements are valuable especially if the improvement in working hours is sustained over several years.

It has been shown that early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis [154]. The disease leads to early consequences in the context of work capacity in the majority of cases, as exemplified by a Swedish study with 15 years of follow-up reporting work disability rates changing from 28% at study start to 44% at 15 years. HAQ was the only factor that remained significant at all time points during the study period [44]. In the present study we found that several of the same factors are important in established RA. For example, disease status measured by HAQ at baseline remained strongly correlated with work ability.

Anti-TNF-treatment has been shown to be highly efficacious in several subgroups of patients, but is also very costly [9,12,18,151]. This makes it a natural candidate for cost-effectiveness analysis with the aim of finding in which patient subgroups their use provides good value for money. When performed from the perspective of the NHS, as recommended by NICE, indirect costs are disregarded. Reimbursement authorities in other countries, e.g. Sweden, require cost-effectiveness analyses to be performed from the societal perspective, including also productivity losses. Direct data on productivity effects of anti-TNF-treatment have henceforth been scarce, and indirect approaches have been used in modelling attempts: evidence of HAQ-reductions while on treatment has been coupled with other data sources showing a relationship between HAQ and productivity [7]. The results from the current study provide direct data indicating that anti-TNF-treatment results in significant gains elsewhere in the societal budget for patients of working age. These data are of importance to inform decision makers facing reimbursement judgments.

The strengths of this study were its long follow-up, population-based design with prospectively collected data and availability to data on all three TNF-antagonists. Its external generalizability is also a strength, as it was based on data from actual clinical practice and patients were not subjected to strict inclusion and exclusion criteria, as in randomized controlled trials.

The study was also afflicted by limitations. Firstly, there was no control group to which the work ability changes could be compared to assess what would have happened without treatment. However, RA is a progressive disease and work ability in RA patients has been shown to be characterized by deteriorating work ability over time

[181]. Still we could demonstrate increases in hours worked. Furthermore, the mean number of hours worked/week in the general population remained stable at approximately 30 hours/week during the study period [182]. In the current study, the overall hours worked/week by RA patients were approximately 10h lower at baseline, a difference that was about halved after treatment initiation.

Mittendorf et al, who did not detect increases in work ability but no deterioration either in an observational study, argued that prevention of further work loss in this patient group may be a worthwhile goal. Hence it is likely that the actual productivity gains are larger than the ones calculated based on the assumption of unchanged work ability over time. There is, however, a risk of effect overestimation in observational studies such as this, if anti-TNF treatment is initiated during a flare, and the observed gain is caused partly by regression to the mean.

Although more patients increased their number of hours worked per week, some also decreased, not only among full time workers. This is not evidence of absence of regression to the mean, but the fact that variations occurred in both directions indicates that treatment initiation did not necessarily happen when work ability was at its minimum.

Secondly, work ability was assessed by self-report. Objective assessment through retrieval of register data could potentially provide better information. It could also provide answers regarding the potential regression to the mean effect, as the long term sick-leave trajectory would be available.

Thirdly, data were only collected while patients were still on anti-TNF-treatment, not after withdrawal. Hence the patients still on drug after five years were not a random sample of the initial population, i.e. differential dropout is likely. Indeed, the productivity gains were greater in continuers than discontinuers, and the results regarding drug cost offsets can only be applied to the selected group of continuers.

Finally, impaired productivity while at work [183] and unpaid work were not assessed in this study.

### **9.3 PAPER III/IV**

In this prospective open-label study we investigated if it was possible to analyze the early day-to-day course-of-disease in patients with RA starting treatment with adalimumab using self-reported data from a PDA and if patient-reported joint counts correlate with physician reported joint counts and if it is possible to use self-reported data to calculate an DAS28 and determine clinical response to a new therapeutic using the EULAR criteria.

A striking and previously unreported finding was the marked day-to-day variability of patient-reported outcomes at baseline. This finding raises a distinct concern pertaining to – most clearly - clinical trials, where baseline data including patient-derived ones are collected only once, with subsequent measures of response being related to those baseline values. In view of our findings it might be more appropriate to request patients

to report such patient-reported outcomes several times over the course of one or two weeks, using the average to form a compiled baseline for comparisons in the follow-up period. This is especially important with one-dimensional instruments such as the VAS. Improvements in hand function and emotional well-being after one week of treatment correlated with improvements in both DAS28 and HAQ after three months, suggesting that these rapid changes could serve as predictors of subsequent therapeutic efficacy. Likewise, one-week improvements in pain, the ability to perform basic activities and the severity of morning stiffness all correlated with the three-month improvement in HAQ. These disease dimensions are not specifically captured by DAS28 and HAQ and thus not regularly measured in clinical trials. However, the possibility to predict treatment outcome at three months already after one week of treatment is obviously of interest.

Several explanations could be considered for the correlation between early improvements in hand function and subsequent improvements in DAS28. Clearly, since 20 of the joints included in the DAS28 are located in the hands a strong relationship between the two outcomes was expected. However, the functional impact of the disease on the smaller joints may respond faster to therapy than other disease aspects. Other possible explanations for the early changes in the hands may be related to the fact the patients were using their hands while handling the PDA, which might emphasize any improvement in hand function from the patients' perspective and it is also possible that questions on a specific symptom may be easier to grasp and relate to than a more general question on disease activity.

Correlations between improvements in hand function and in HAQ have been demonstrated in several studies. Both Björk et al and Eberhardt et al found that the specific measure of hand function Signals of Functional Impairment (SOFI), grip ability test (GAT) and grip force correlated significantly with HAQ [184, 185]. Our data are in line with these studies since improvements in hand function and basic activities correlated with improvements in HAQ. However, ours is the first study to demonstrate that improvements in hand function precede and, as it were, predict those in overall disease activity and function.

There was an excellent correlation between patient reported joint counts correlated and physician joint counts at both baseline and at three months follow-up, although the correlation at follow-up was lower than at baseline. The latter finding could be attributed to the low levels of swollen and tender joints in many patients following treatment the impact of a one-joint difference becoming disproportionately large in that case. As shown in previous studies [186-188] the correlation was lower for swollen joint counts than for tender joint counts reflecting the difficulty for an untrained person to distinguish between a true swollen joint and a joint that is enlarged due to other reasons (bony deformation, swelling of other structures near the joint etc). However, using patient-reported joint counts resulted in similar improvements in DAS28 as when using physician-reported joint counts. Physician global VAS and HAQ correlated with joint counts regardless of reporter at both baseline and follow up. The correlation between joint count and physician global VAS increased during the study period for both patient reported and physician reported data.



Patient reported joint counts have been studied previously and have been found to be reproducible [186,189] and correlate with physician reported joint counts as well as be responsive to natural changes in disease activity [186]. The reliability of patient reported joint counts improves when patients receive a simple training [187]. In our study the patients did not receive any training but most of the patients had established RA which may explain the excellent correlation. The fact that in patients with early RA the correlations were weaker suggests that patients learn to recognise a true swollen joint with time. Our study also suggests that patient reported joint counts are as sensitive to treatment response as physician reported joint counts as the number of patients with good or no EULAR response did not differ at the group level. However there were some differences at the individual level, many of them for patients close to the cut offs. Another advantage of using patient-reported data is the possibility of an increased reproducibility with the patient being the sole reporter. Especially since most clinical trials and clinical research studies in RA require that the joint count is performed by the same observer at each assessment due to lack of reproducibility between physicians [190]. Using patient-derived joint counts might also save time in the patient-physician encounter although this was not measured directly in our study.

The use of digital assistants to collect patient self-reported data has been validated in patients with stable RA [191-193]. In a recent review on studies comparing PDAs to pen and paper the former were found to outperform the latter in the collection of patient data. The PDA method led to improved protocol compliance and PDAs were preferred over pen and paper although the number of missing data may be higher due to technical problems [194]. The patients in our study had no problems in accepting or using the PDA as a way of collecting self-reported data, in fact several of the patients reported more frequently than requested (omitted in the analyses) and expressed appreciation over the instrument.

The prospectively collected data from a well defined population is one of the strengths of this study. The external generalizability was high as the study was based on data from actual clinical practice and patients were not subjected to strict inclusion and exclusion criteria, as in randomized controlled trials. The fact that it was possible to measure treatment response accurately when using patient reported joint counts is the key result from this study. EULAR response by patient reported data was accurate and in concordance with EULAR response by physician reported data. The study also had limitations. Firstly, there was no control group to which the improvements could be compared. There is, also, a risk of effect overestimation in observational studies such as this, if anti-TNF treatment is initiated during a flare, and the observed gain is caused partly by regression to the mean.

Being both time-saving and capturing the fluctuations of the disease progress without risk of recall bias the use of PDAs or other digital instruments (such as websites [193]) could be very helpful in clinical practice. In the future patient self-reported data could be linked to the patient records giving the treating physician a regular update on disease status without the time consuming logistics of a scheduled visit/phone consultation.

## **10 CONCLUDING REMARKS AND FUTURE PERSPECTIVES**

The development of biological agents has been a major breakthrough in the treatment of RA and other types of inflammatory arthritis such as psoriatic arthritis and ankylosing spondylarthritis as well as other autoimmune diseases such as Crohn's disease. TNF-inhibitors for the treatment of RA have been extensively studied in RCTs, open-label extension studies, strategy trials as well as registry studies, all of which have given important contributions regarding the efficacy and safety of these agents. Careful evaluation at treatment initiation and long-term surveillance of the patients will continue to be important to monitor the TNF-inhibitors place in the treatment strategy of RA.

A distinct concern is represented by the high cost of these agents. As the biological therapies that are now available for RA and other diseases are generally needed chronically in these substantial patient populations, an ongoing debate regarding cost-effectiveness will be required with input from clinicians, patients, government and the community. Our study on work-force participation gives promising indications that the money may be very well spent. The increase in work-force participation over up to five years in a group of patients typically expected to experience progressively deteriorating work ability could lead to significant indirect cost benefits to both patients and society.

Other possibilities to cut direct costs may very well lie in developments in biotechnology which may decrease production costs. In the longer term, the growth in understanding of pathological mechanisms underlying RA at the genetic and environmental level as well as the molecular and cellular level has triggered an avalanche of new biological therapies for this disabling disease and there is hope that the current biologic agents such as the TNF-inhibitors will eventually be replaced by even more effective, safe and cost-effective therapies.

The opportunity to treat newly diagnosed RA aggressively in the early phase of the disease and subsequently withdraw the treatment if the patient reaches remission is exciting and may lead to further increases in quality of life at a lower direct cost. This however needs to be studied more extensively and with a sufficient length and form of follow-up. The inclusion of patient-reported data on joint status and other health measurements through digital solutions such as the internet would be both time-saving and give early and accurate information on the fluctuations of the patients individual disease progress without risk of recall bias. If linked to the patient records patient-reported data could give the treating physician a regular update on disease status without time consuming logistics, for both patient and physician, of a scheduled visit/phone consultation.

Registries and observational studies offer an excellent opportunity to study the effects of different treatment strategies in a clinically relevant setting, with full information on and naturalistic managing of concomitant medication etc. The experiences from these studies will lead to a more safe and effective use of the available agents.

## 11 SVENSK SAMMANFATTNING

Reumatoid artrit (RA) är en kronisk inflammatorisk ledsjukdom som karaktäriseras av smärta, stelhet och svullnad i lederna samt en tilltagande funktionsnedsättning allteftersom sjukdomen framåtskrider. Sjukdomen förekommer hos ca 1 % av befolkningen och den drabbar i större utsträckning kvinnor än män (3:1). Karaktäristiskt för sjukdomen är inflammation av synovialmembranet (ledernas tunna inre hinna), men även andra organsystem (som tex lungsäck, njurar, blodkärl mfl) kan drabbas. I den inflammatoriska processen frisätts proinflammatoriska signalsubstanser, cytokiner, som ytterligare driver på inflammationen vilket leder till skador på ledens brosk, senor och ben. De skador som uppstår i brosk och ben kan noteras via röntgenundersökning, och de flesta patienter har röntgenförändringar redan inom ett eller ett par år från symtomdebut. Sjukdomens förlopp är mycket individuellt med olika grad av leddestruktion och funktionsnedsättning. Sjukdomens effekter är således omfattande och resulterar inte bara i en sänkt livskvalitet för den enskilda patienten utan innebär även stora kostnader för samhället i form av produktionsbortfall och sjukvårdsbelastning.

På senare tid har det tack vare utvecklingen inom den biomolekylära teknologin tillkommit nya möjligheter att behandla RA i och med möjligheten att kлона de cytokiner och receptorer som är involverade i den inflammatoriska processen och därmed producera proteiner som specifikt motverkar deras effekt. Dessa läkemedel kallas med ett samlingsnamn biologiska läkemedel. Den största nackdelen med samtliga biologiska läkemedel är de höga kostnaderna. Ett års behandling kostar ca 140 000 kr i rena läkemedelskostnader. Den kostnaden bör dock inte vägas enbart mot den påtagliga förbättringen i livskvalitet för patienterna, utan även mot vinster i form av minskningar i andra sjukvårdskostnader (i synnerhet i samband med operationer), minskad funktionsnedsättning, och därmed ökad arbetsförmåga, och ökat oberoende av samhällets övriga resurser. Den här avhandlingen omfattar Enbrel (etanercept), Humira (adalimumab), och Remicade (infiximab) som verkar genom att binda upp TNF (tumör nekros faktor alfa, en av många proinflammatoriska cytokiner) och förhindra dess bindning till receptorer och därigenom motverka dess biologiska effekter.

Huvudsyftet med den här avhandlingen är att undersöka hur dessa läkemedel fungerar i en vanlig patientpopulation hämtad från STURE-registret i Stockholm som är en del av det nationella registret ARTIS. De patienter som ingår i kliniska prövningar av läkemedel motsvarar tyvärr inte alltid den kliniska verkligheten. Exklusionskriterierna utesluter ofta patienter med mer än en sjukdom, hög ålder (eller för all del även låg ålder) och andra faktorer som kan störa utfallet. Detta gör att den information man får av prövningarna är begränsad och ytterligare uppföljning behövs för att kunna visa den sanna bilden av ett läkemedels effekter. Genom att följa patienterna prospektivt i ett register får man full insyn i övriga co morbiditeter, läkemedelsbehandling mm som kan påverka behandlingsresultatet.

I den första studien har vi undersökt möjliga riskfaktorer till infusionsreaktioner vid behandling med infiximab. Vi fann att samtidig användning av Prednisolon (kortison) hade en skyddande inverkan medan hög funktionspåverkan, förhöjd sänka, hög

sjukdomsaktivitet och behandling med flera sjukdomsmodifierande läkemedel innan behandlingen med infliximab alla bidrog till att öka risken för infusionsreaktioner. Glädjande nog har antalet infusionsreaktioner minskat med åren, vi kan bara spekulera i orsaken till detta men troligen är det tätt sammankopplat med en ökad erfarenhet hos behandlande läkare och sjuksköterskor.

I den andra studien har vi undersökt huruvida arbetsförmågan påverkades av behandling med TNF-blockare. Patienter mellan 18 och 55 år ingick i studien och data från deras första behandling med TNF-blockare (det är relativt vanligt att patienterna kan ha behandlats med mer än en TNF-blockare) analyserades. Vi fann att arbetsförmågan ökade med i snitt 4 timmar/vecka (från i medeltal 20 timmar/vecka) under det första behandlingsåret och varje efterföljande behandlingsår gav ytterligare 30min/vecka. Ökningen i arbetsförmåga speglades av en motsvarande minskning i sjukdomsaktivitet och smärta samt en ökad funktionsförmåga. Då arbetsförmågan i allmänhet minskar pga RA så är detta mycket glädjande både för den enskilda patienten och för samhället då produktionsbortfall är den enskilt största kostnaden för RA.

I studie tre och fyra har vi följt patienterna mycket intensivt under de tre första månaderna av behandling med adalimumab. Vi har dessutom undersökt om självrapporterade data från den första behandlingsveckan kan prediktera behandlingssvar vid tre månader samt om självrapporterad ledstatus korrelerar med den ledundersökning som doktorn gör. För att mäta tidiga behandlingseffekter utrustades patienterna med handdatorer och fick svara på frågor om sin hälsostatus med täta intervall, ledstatus fick de rapportera in innan behandlingsstart samt vid tre månader. Redan efter en vecka såg man signifikanta förbättringar i flertalet av de självrapporterade uppgifterna. Förbättring i handfunktion, förmåga att klara av basala aktiviteter, trötthet och emotionellt välmående korrelerade med en positiv behandlingseffekt efter tre månader. I framtiden skulle dylika uppgifter kunna användas till att på ett tidigare stadium fatta beslut om aktuell behandling. Självrapporterad ledstatus överensstämde med den undersökning som behandlande doktor gjorde både innan behandlingsstart och vid tre månader. Möjligheten för patienten att själv lämna uppgifter om sin ledstatus har flera fördelar. Dels minskar variabiliteten då det är samma person som utför undersökningen, dels är det tidsbesparande; patienten kan själv ringa in och meddela sin ledstatus till behandlande doktor som utifrån detta kan fatta beslut om ett besök är nödvändigt eller ej.

Sammanfattningsvis så bekräftar resultaten i denna avhandling att TNF-blockare utgör en effektiv behandling av RA. Vi har dessutom visat på potentiella fördelar med avseende på ökad arbetsförmåga samt utforskat möjligheten att tidigt få information om behandlingseffekt genom självrapporterade data. Registerstudier är ett utmärkt verktyg för att undersöka behandlingseffekter i en kliniskt relevant miljö, fortsatt uppföljning av samtliga biologiska läkemedel kommer att ge värdefull kompletterande information om deras plats i behandlingsstrategin för RA.

## 12 ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to the following people who have supported me throughout my PhD studies:

**Ronald van Vollenhoven** my main supervisor for all your support and patience while showing me how to think, work and write like a scientist and guiding me through the labyrinth of PhD studies. For always taking time to listen and give constructive feedback and sharing your thoughts on both life and science with me. I have learned so much from you and I will always be grateful.

**Staffan Eksborg** my co supervisor and statistical coach. For your support and enthusiasm even in the smallest of matters. For always being there with a word of advice – even the ones I didn't want to hear at the time – and a contagious laugh to get me through the day. I hereby promise to never use a comma in a table ever again!

**Lars Klareskog** my co supervisor for creating a good scientific atmosphere at the clinic and for making it possible for so many students to be introduced to the world of science.

Present and former Heads of the Rheumatology Clinic **Johan Bratt** and **Ralph Nisell** for assuring a positive working atmosphere and support. A special thanks for the opportunity to work clinically with patient education, it has been so much fun and also a great learning experience.

**Seija Johansson** for making me feel so welcome at the clinic that first scary day in the autumn of 2001. Without your kindness and support I would never have discovered the intriguing world of rheumatology. Thank you!

**Apoteket AB** and **Apoteket Farmaci AB** for supporting me financially.

**Ulrika Aronowitsh** for making it possible to conduct my research as part of my ordinary employment. For moral support in difficult carrier decisions and an extra thanks for style advice when it comes to really important things such as shoes and handbags.

My co-authors **Sofia Ernestam, Martin Neovius, Lennart Jacobsson, Ingemar Petersson, Solbritt Rantapää-Dahlqvist, Annika Teleman, Jan-Åke Nilsson, Cheryl Cullinane-Carli, Thorunn Jonsdottir, Eleanor Gullström**. I have learned so much from you, thank you!

**Colleagues and friends at the clinic** for creating a good working environment and making the Rheumatology Unit such an exciting and enjoyable place to work. I will miss you all! A special thanks to **UD**: Birgitta and Cheryl for nice talks on science and life in general and to the **Rheumachor** for making my last semester at the clinic a harmonic one (at least every once in a while ☺)

**Gunnel Bemerfeldt** and **Susanne (Doris) Karlfeldt** for always giving excellent support and for being so patient with all my questions.

**Friends and colleagues at Apoteket/Apoteket Farmaci**

Carin, Christine, Ingrid, Karin, Malin och Nima för stöd och bollplankssupport både vad det gäller arbetet och balansen med privatlivet. LIC (“past and present”☺) Gunilla, Eva, Mohammad, Ali, Therese, Leif och Åsa. Ett särskilt tack till Leif för kloka råd kring livet och till mina sambos Åsa och Therese för stöd och skratt under långa arbetsdagar. ”Forsken”, tack för stöd och uppmuntran och utfodring med godis under förmiddagsfikat, Carina: keep smiling och glöm inte tandtråden! ☺

**Friends (or rather extended family):**

Mina kära vänner: Tack för att ni alla påmint mig om livet utanför forskningsbubblan, jag är så glad att det nu (äntligen!) finns mer tid för lek och umgänge!

Ett speciellt tack till: **Erika, Lee, Karin, Martina** och **Anna** från de gyllene åren på Göteborgs Nation. Är det verkligen flera år sedan vi hade mellanfester i korridoren, dansade runt Snerkes, gick på Lökmiddagar och lördagsfikade tills köket var tomt? Chokladvänner i nöd och lust: **Linnea, Lojs** och **Tesan** må vi alltid fortsätta att undersöka exakt hur mycket vin, oliver och choklad man kan inta på en kväll. Jag tror svaret kräver mångåriga studier (tack och lov!).

**Family**

**Yvonne, Tommy, Maria** och **Johan** ni är världens bästa extrafamilj. Det känns så lyxigt att ha fått er ”på köpet”.

**Mamma** och **Pappa** stort tack för alla godnattsagor när jag var liten! De lärde mig att vara nyfiken på allt och alla! Tack för att ni alltid tror och lyssnar på mig i stort och smått. **John**, bror och vän, nu kanske jag hinner bjuda på middag någon gång ibland ☺. Tack för att du vidgar mina vyer inom humaniora!

**Daniel**, Master of Excel, mästerkock, privat datakonsult, coach, bästa vän och underbar make. Tack för allt stöd såväl själsligt som rent handgripligt när datafilerna och jag var osams. Tack för alla roliga saker du får mig att prova när jag tror att jag inte törs, tack för världens godaste lasagne och för att du alltid finns där. Utan dig skulle detta aldrig ha gått vägen! Puss!

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