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From the Department of Rheumatology

Anti-TNF treatment of chronic arthritis in clinical practice

New assessment method and predictors of efficacy and tolerability

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av

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Anti-TNF treatment of chronic arthritis in clinical practice

New assessment method and predictors of efficacy and tolerability

Abstract

Treatment of chronic inflammatory arthritis has undergone major changes over the past years following introduction of targeted biological therapies. Tumour necrosis factor (TNF) blocking therapy has been the most important biological treatment of chronic arthritis to date.

The overall objective of this thesis was to develop a new assessment method of efficacy of biological therapy in clinical practice. Further objectives were to study efficacy and tolerability and predictors thereof in anti-TNF treated patients with chronic arthritis in an open study setting. The thesis is based on four studies of patients with established rheumatoid arthritis (RA) and a study of patients with psoriatic arthritis (PsA).

Patients included in the five studies were monitored according to a standardized clinical protocol of the South Swedish Arthritis Treatment Group (SSATG) developed at the Department of Rheumatology in Lund. The protocol included baseline characteristics such as diagnosis, disease duration, previous and ongoing disease modifying antirheumatic drugs (DMARDs), treatment start and termination. In addition efficacy measures used for calculating treatment response, i.e. EULAR and ACR response criteria, were collected at fixed time-points. Data were prospectively registered from March 1999.

To overcome shortcomings of previous methods for reporting response data from long term observational cohorts, LUNDEX (LUND Efficacy indeX) was designed. LUNDEX adjusted response data simply combines the proportion of patients fulfilling a selected response criterion with the proportion of patients adhering to a particular therapy. LUNDEX applyed on RA and PsA patients proved to be a valuable tool for evaluating drug efficacy in observational studies. It has the advantage of integrating both clinical response as well as adherence to therapy in a composite value.

Predictors of drug survival in RA and PsA were studied using Cox regression models. The models showed that the risk for premature treatment termination were higher in infliximab treated patients than for etanercept. Also, regression analysis showed that patients with higher baseline CRP-levels and concomitant MTX treatment had better overall treatment continuation. Treatments with concomitant MTX or other DMARDs as well as low disability were associated with good response to anti-TNF therapy in RA.

Moreover, RA patients who failed their first course of anti-TNF treatment, showed response rates in the range of the initial treatment course. In contrast, response to a third anti-TNF treatment was markedly reduced, suggesting that other treatment options should be tried.

In conclusion, LUNDEX proved to be a practical and a potential universal tool, valuable for assessing drug response in an open study setting. Important predictors of efficacy and tolerability of anti-TNF treatment were identified.

Key words

Arthritis, rheumatoid arthritis, psoriatic arthritis, TNF antagonists, response, drug survival, adverse events

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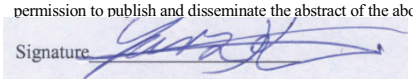
Signature 

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Anti-TNF treatment of chronic arthritis in clinical practice

New assessment method and predictors of efficacy and tolerability

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CONTENTS

Abstract 2
List of Publications 3
Abbreviations 4
Introduction 5
Rheumatoid arthritis 5
Epidemiology 5
Clinical symptoms, diagnosis and classification 6
Assessment of disease activity and function 7
Psoriatic arthritis 9
Epidemiology 9
Clinical symptoms, diagnosis and classification 9
Assessment of disease activity and function 11
Pharmacological treatment of rheumatoid arthritis and psoriatic arthritis 12
Conventional DMARD treatment 12
Glucocorticoids 13
Biological treatments 13
Treatment recommendations 14
Observational studies and randomized controlled trials 16
Strengths and weaknesses 16
Aims of the present investigation 17
Protocol, study population and methods 18
The SSATG database 18
Study population 19
Methods 21
Statistics 23
Results and discussion 24
The LUNDEX concept 24
LUNDEX adjusted and per protocol response data in rheumatoid and psoriatic arthritis 25
Drug adherence and predictors thereof in reumatoid arthritis and psoriatic arthritis 27
Predictors of treatment response to anti-TNF therapy in rheumatoid arthritis 31
Response rates and predictors in rheumatoid arthritis patients switching anti-TNF therapy 33
Serious adverse events in anti-TNF treated psoriatic arthritis patients 35
Conclusions 37
Perspectives for the future 38
Popularized summary in Swedish 39
Acknowledgements 40
References 41
Papers I-V 47

Abstract

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To overcome shortcomings of previous methods for reporting response data from long term observational cohorts, LUNDEX (LUND Efficacy indeX) was designed. LUNDEX adjusted response data combines the proportion of patients fulfilling a selected response criterion with the proportion of patients adhering to a particular therapy. LUNDEX applied on RA and PsA patients proved to be a valuable tool for evaluating drug efficacy in observational studies. It has the advantage of integrating both clinical response as well as adherence to therapy in a composite score.

Predictors of drug survival in RA and PsA were studied using Cox regression models. The models showed that the risk for premature treatment termination was higher in infliximab compared to etanercept treated patients. Also, regression analysis showed that patients with higher baseline CRP-levels and concomitant MTX treatment had better overall treatment continuation.

Good response to anti-TNF therapy in RA was associated with concomitant MTX or other DMARD treatment as well as low disability. Moreover, RA patients who failed their first course of anti-TNF treatment, showed response rates during second anti-TNF treatment course in the range of the initial treatment. In contrast, response to a third anti-TNF treatment was markedly reduced, suggesting that other treatment options should be tried.

In conclusion, LUNDEX proved to be a practical and a potentially universal tool, valuable for assessing drug response in an open study setting. Important predictors of efficacy and tolerability of anti-TNF treatment were identified.

List of Publications

The current thesis is based on the following five papers, which will be referred to in the text by their Roman numerals:

I The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden.
Kristensen LE, Saxne T, Geborek P.
Arthritis Rheum 2006; 54:600–606

II Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden.
Kristensen LE, Saxne T, Nilsson JA, Geborek P.
Arthritis Res Ther 2006; 22:8:R174

III Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established rheumatoid arthritis: Results from the South Swedish Arthritis Treatment Group Register.
Kristensen LE, Kapetanovic MC, Gülfe A, Saxne T, Söderlin MK, Geborek P.
Rheumatology 2007, accepted

IV Treatment Response to a Second or Third TNF-inhibitor in RA: Results from the South Swedish Arthritis Treatment Group Register.
Karlsson J, Kristensen LE, Kapetanovic MC, Gülfe A, Saxne T, Geborek P.
Rheumatology 2007, accepted

V Efficacy and tolerability of anti-TNF therapy in psoriatic arthritis patients: Results from the South Swedish Arthritis Treatment Group Register.
Kristensen LE, Gülfe A, Saxne T, Geborek P.
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Abbreviations

ACR	American College of Rheumatology
ANA	antinuclear antibodies
Anti-CCP	anti-cyclic citrullinated peptide
AS	ankylosing spondylitis
CDAI	clinical disease activity index
CRP	C-reactive protein
DAS	disease activity score
DAS28	disease activity score based on 28-joint count
DMARDs	disease modifying anti rheumatic drugs
ESR	erythrocyte sedimentation rate
ESSG	The European Spondylarthropathy Study Group
EULAR	European League Against Rheumatism
HAQ	health assessment questionnaire disability index
HLA	human leukocyte antigen
IL-1	interleukin1
IL-1Ra	interleukin1 receptor antagonist
LUNDEX	LUND Efficacy indeX
MTX	methotrexate
NSAIDs	non-steroidal anti-inflammatory drugs
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RCT	randomised clinical trial
RF	rheumatoid factor
SAE	serious adverse events
SDAI	simplified disease activity index
SpA	spondarthritis
SSATG	South Swedish Arthritis Treatment Group
TNF	tumour necrosis factor
VAS	visual analogue scale
WHO	World Health Organisation

Introduction

Treatment of chronic inflammatory arthritis has undergone major changes over the past years following introduction of biological therapies. Tumour necrosis factor (TNF) blocking therapy has been the most important biological treatment of chronic arthritis to date. Initially, TNF antagonists were approved for treatment of rheumatoid arthritis (RA). However, the approved indication has subsequently expanded to also include treatment of psoriatic arthritis (PsA), ankylosing spondylitis (AS), and juvenile idiopathic polyarthritis.

Arthritis in RA is often symmetric and typically affects smaller joints of the extremities. AS often involves the spine, but enthesophaties and dactylitis are also common symptoms. PsA is joint inflammation associated with psoriasis of the skin or nails. Juvenile idiopathic arthritis starts before the age of 16 and may present in many different ways. The clinical symptoms vary between these different types of arthritis but those related to inflammation such as fatigue and joint pain are common and are often the dominating symptoms.

This thesis consists of 4 studies of patients with established RA and a fifth study of patients with psoriatic arthritis. The overall purpose of this investigation was to develop a new assessment method of efficacy of therapy in clinical practice. Also we wanted to study predictors of efficacy and tolerability of anti-TNF treatment in patients with established arthritis in an open study setting.

Rheumatoid arthritis

Epidemiology

RA is a chronic inflammatory disease mostly affecting the peripheral smaller joints of the body. RA is globally present affecting ethnic groups with different prevalence; however, in total it is the most common inflammatory joint disease. A rate of 0.5-1% of the Swedish population was reported (Simonsson et al.1999) analogous to the prevalence rates in other part of the western world. Prevalence rates as high as 5% has been found among some North American Indians (Hirch et al. 1998, Jacobsson et al. 1994) and the lowest prevalence was reported among countryside populations of China, Indonesia and Africa (Silman et al. 1993a, Symmons 2002). The incidence of RA is in the region of 3 cases per 10,000 population per annum (Rantapää and Jacobsson 2005). The estimated female to male prevalence in RA is 2.5:1 (Lawrence et al. 1998), and symptoms of RA tend to be reduced during pregnancy and often relapses in the postpartum period (Silman 2002) indicating a significant role of sex hormones. Moreover, women taking oral contraceptives seem to have decreased risk of developing RA (Silman 2002).

The genetic role in RA has been investigated based on twin studies, where genetic factors has been estimated to account for about 60% of the risk for developing RA (MacGregor et al. 2000). Monozygotic twin studies reported concordance rates of about 15% (Silman et al. 1993b). The HLA-class II alleles have been documented as important genes. Especially HLA-DRB1 alleles encoding the "shared epitope" are associated with susceptibility for developing RA.

Smoking is the single most important environmental factor that has been linked to RA (Vessey et al. 1987, Silman et al. 1996). Furthermore, studies on gene-environment interactions have shown that presence of the shared epitope genes in combination with smoking provides an even higher risk of developing seropositive RA (Padyukov et al. 2004). Interestingly, a recently proposed model for the development of RA has shown positive interaction between smoking, immune reactions to citrullinated proteins, and the shared epitope increasing the risk of RA development (Klareskog et al. 2006). This important study illustrates the complex multifactor interaction of genes, environmental

factors and immunology in the development of RA, and to date the exact aetiology of RA remains an enigma.

Clinical symptoms, diagnosis and classification

RA is a syndrome with no single clinical sign, symptom or test that can establish the diagnosis. Consequently RA is diagnosed based on the combination of typical signs and symptoms. The natural course of RA is undulating and symptoms may come and go, depending on the degree of tissue inflammation. When the disease is active (a flare), symptoms can include morning stiffness of muscles and joints, lack of appetite, weight loss, low grade fever, pain, and fatigue (Rantapää and Jacobsson 2005). Arthritis is a hallmark of disease flares. The synovium of the joint becomes inflamed, resulting in thickening and production of excessive joint fluid. When tissue inflammation subsides, the disease is inactive (in remission). Remissions can occur at different intervals with treatment and at rare occasions spontaneously. During remissions, symptoms of the disease disappear, and patients generally feel well. The course of RA varies from patient to patient, and periods of flares and remissions are typical. Moreover, disability due to cumulative joint destruction is another feature that can dominate later during the course of RA, and should be closely monitored and preferably prevented. It should be noted that RA is a systemic disease, sometimes also affecting extra-articular tissues throughout the body including the skin, blood vessels, heart, lungs, and salivary glands (Turesson et al. 2002).

Early in the course of RA many patients present symptoms of an undifferentiated polyarthritis (Dixon and Symmons 2005), making the diagnosis difficult. However, early identification and referral to a rheumatologist is crucial for achieving optimal treatment and prognosis for the patient. Therefore recommendations have been developed to serve as clinical guidelines for general practitioners for early identification of patients likely to have RA (Emery et al. 2002a and b). These recommendations consist of the presence of any of the following symptoms: ≥3 swollen joints, involvement of metacarpophalangeal or metatarsophalangeal joints or morning stiffness ≥ 30 minutes.

The American College of Rheumatology (ACR) has developed a set of classification criteria for established RA to be used in clinical studies and not for managing the individual patients (Arnett et al. 1988). According to the ACR revised criteria for classification of RA 4 out of 7 of the criteria must be present during a period of at least 6 weeks before a patient can be classified as having RA, table 1.

Table 1: The American College of Rheumatology 1987 revised criteria for RA

- Morning stiffness of >1 hour most mornings for at least 6 weeks.
- Arthritis and soft-tissue swelling of >3 of 14 joints/joint groups
- Arthritis of hand joints
- Symmetric arthritis
- Rheumatoid nodules
- Rheumatoid factor positivity
- Radiological changes suggestive of joint erosion or periarticular osteopenia in hand/wrist joints

Later in the course of RA the disease is commonly associated with several co-morbidities. Cardiovascular diseases, malignancy, peptic ulcer disease and chronic lung diseases are the most common co-occurring diseases (Gabriel et al. 1999). Recently, several studies have reported increased cardiovascular morbidity in patients with RA (Gabriel et al. 2003, Turesson et al. 2004). Especially, RA patients have an increased risk of developing malignant lymphoma associated with disease activity (Baecklund et al. 1998). It should be noted that treatment with DMARDs in RA does not increase the risk of developing lymphoma in patients with high disease activity (Baecklund et al. 2006). Risks of cancers in RA patients treated with TNF-antagonists are still debated, but were in general rather similar to those of RA patients not receiving TNF blockers (Askling et al. 2005a and b). A somewhat higher risk for malignancies in general during TNF-blocker treatment has been reported by Bongartz et al. 2006, whereas increased risks of lymphomas has been reported by Geborek et al. 2005a. However, studies reporting increased risks of malignancies include patients from the early era of anti-TNF treatment, thus representing patients with a highly accumulated load of inflammation.

In addition, Askling et al. conducted a study on risks of solid cancers in the Inpatients Register Cohort of patients with RA in Sweden and found a marginally increased overall risk for smoking related cancers and non melanoma skin cancers but decreased risk for breast and colorectal cancers (Askling et al. 2005b).

Additionally, RA patients have increased incidence of infections compared with age-matched subjects without RA (Doran et al. 2002). This might be explained by immune dysfunction associated with the disease itself, co-morbidity and/or concomitant medication such as immunosuppressive drugs.

Assessment of disease activity and function

Assessment of disease activity and function is among the greatest challenges in the care of patients with RA, and there is no single unifying test or measure for such assessment. As mentioned above, the disease activity plays a central role in causing disability and naturally an evaluation thereof is important to predict the outcome and efficacy of therapeutic interventions during follow-up. A core set of variables reflecting disease activity has been recommended both in clinical trials and observational studies (Bertinotti et al. 2006). Such variables may also be used in daily clinical practice (van Riel et al. 2001). The core set consists of seven disease activity measures: tender joint count, swollen joint count, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function and ESR or C-reactive protein (CRP) evaluation.

Other measures, such as X-ray changes, ultra sound, and MRI might be useful in clinical trials, but not feasible in daily clinical practice. In addition, quality of life instruments (Ortiz et al. 1999), as well as the social and economic aspects of rheumatic diseases are important issues to evaluate.

Patients and or doctors subjective assessment is scored using a continuous visual analogue scale (VAS) or a pointed Likert scale. Assessment of function is covered by the Stanford Health Assessment Questionnaire (HAQ)-Disability Index (Ramey et al. 1992, Bruce et al. 2003a and b). It reflects the patient's self-reported assessment of function, and has been proven to be valid for the assessment of functional disability in RA patients.

The combination of core set variables constitute two different sets of improvement criteria used in clinical trials: the preliminary American College of Rheumatology (ACR) improvement criteria (Felson et al. 1995) consisting of all seven core set variables and the European League Against Rheumatism (EULAR) response criteria based on the disease activity score (DAS) using 4 core set variables (van Gestel et al. 1996).

According to the ACR20 improvement criteria treatment response is defined as a 20% improvement

in tender and swollen joint count and 20% improvement in 3 of the remaining core set parameters. Likewise, ACR50, ACR70 and ACR90 correspond to 50%, 70% and 90% improvement. The EULAR response criteria are based on changes in the DAS, and include not only changes in disease activity, but also current disease activity. DAS is an index including tender joint count, total number of swollen joints, erythrocyte sedimentation rate (ESR) and the patient's general health assessment scored on a VAS. The original DAS was developed using graded tender joint count and 44 swollen joint count (van der Heijde et al. 1990). However, a simpler and equally valid DAS using 28 joint count for tenderness and 28 joint count for swelling (DAS28) has substituted the original DAS (Prevoo et al. 1995, van Riel et al. 2000, http://www.das-score.nl).

The DAS28 score indicates the current disease activity on a scale between 0 and 10. High disease activity corresponds to a DAS28 above 5.1; moderate 3.2-5.1; low <3.2; remission is defined as DAS28 <2.6. EULAR responses require both absolute DAS scores as well as relative changes.

Recently, simplifications of the DAS have been introduced as the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) (Aletaha and Smolen 2005). These disease activity indices reflect the numeric sum of 5 and 4 outcome variables, respectively. SDAI, CDAI, and absolute DAS scores have the advantage of helping patients to better understand their disease activity status, because they represent an intuitive response (single number) (Aletaha and Smolen 2005). Moreover, outcome measures defined by absolute values might be transferred from clinical trials to everyday clinical practice, permitting a feasible, and reproducible method to evaluate RA status and response to therapy on an individual patient level, allowing physicians to optimize the treatment (Bertinotti et al. 2006). Core set variables included in the composite response criteria or disease activity indices are displayed in table 2.

Table 2: The relation between core set variables and composite response criteria or disease activity indices (modified from Gülfe et al 2005).

Criteria set	Core sets							
	Tender joint count	Swollen joint count	Patient global VAS	Patient pain VAS	Evaluator's global	HAQ	ESR	CRP
ACR	+	+	+/-	+/-	+/-	+/-	+/-	+/-
EULAR (DAS)	+	+	+	-	-	-	+	+*
CDAI	+	+	+	-	+	-	-	-
SDAI	+	+	+	-	+	-	-	+

+ = included; – = not included; +/- = any three of the five core sets must be included; ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS, disease activity score; * = DAS might be calculated based on CRP; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire; SDAI, simple disease activity index; VAS, visual analogue scale.

Finally, adherence to therapy (drug survival or drug retention rate) can be used as a surrogate measure of effectiveness in long-term observational studies. Drug survival measures the length of time a patient continues to take a particular drug. It is a well established measure of drug effectiveness, which encompasses factors such as adverse drug reactions and side-effects, poor compliance, clinical efficacy and others (Wolfe 1995). Adherence to therapy is simply measured by registering when the patient starts on a new medication and noting the date and preferably the reason why they stop taking the medication.

Psoriatic arthritis

Epidemiology

Psoriatic arthritis (PsA) is a chronic arthritis associated with psoriatic skin disease. PsA affects around 5-7% of people suffering from the chronic skin condition psoriasis. However, prevalence rates vary substantially, from 5 and up to 42% of patients with psoriasis, depending on the source of literature consulted (Gladman et al. 2005, Zachariae 2003). This disagreement reflects the lack of sufficient diagnostic criteria. Likewise, the reported incidence of PsA has also varied from 3.4 to 8 per 100 000 (Gladman et al. 2005). Psoriatic arthritis traditionally belongs to the group of spondarthritis together with ankylosing spondylitis (AS), reactive arthritis, arthritis associated with inflammatory bowel diseases, juvenile and undifferentiated spondarthritis (Khan 2002). Typical for this group is an association with tissue type HLA-B27, seronegativity for rheumatoid factor, and axial joint involvement. Psoriatic arthritis can develop at any age, however on average it tends to appear about 10 years after the first signs of psoriasis (Gladman 1995). For the majority of people this is between the ages of 30 and 50, but it can also affect children. Men and women are equally affected by this condition. In about one in seven cases the arthritis symptoms may occur before any skin involvement (Gladman 1995). The exact cause of psoriatic arthritis is unknown, but about 40% of people with psoriasis or psoriatic arthritis have a close relative with the same condition, indicating that both environmental and genetic factors play important roles.

Clinical symptoms, diagnosis and classification

The study of PsA is difficult and has lagged behind the study of other chronic arthritis, since no validated diagnostic criteria exist (O'Neill and Silman 1994). Also many different classification criteria have been launched over the past 30 years, and therapeutic studies of PsA could therefore potentially include heterogeneous patient samples (Helliwell and Taylor 2005). As a consequence, clinical symptoms may vary depending on the classification criteria used. However, symptoms related to joint inflammation are common features in active psoriatic arthritis. Thus, affected joints may be swollen and painful and general symptoms such as fatigue and loss of appetite is also a classic feature. Psoriatic arthritis commonly affects the distal joints of the fingers and toes. It can also affect larger joints, such as the hips and knees and about a third of patients with psoriatic arthritis also have a stiff painful lower back or neck. Another common hallmark is enthesitis and dactylitis, which are painful inflammations of tendon insertions and sausage-like swelling of the digits, respectively. Many of patients with psoriatic arthritis will have psoriatic nail lesions characterized by pitting of the nails, transverse depressions, subungual hyperkeratosis, or more extremely, loss of the nail itself (Gladman 1995). A clinical entity often grouped with psoriasis is pustulosis palmaris et plantaris (PPP). In 1996, Mejjad et al. reported that arthritis associated with PPP and classic PsA can be distinguished by their radiological manifestations (Mejjad et al. 1996). The anterior chest wall, especially the sternoclavicular joints, is more frequently involved in pustulotic arthritis than in PsA, both clinically and radiologically. Sternoclavicular joints generally appear with erosive lesions in PsA but with large ossifications in PPP. When PPP is associated with synovitis, acne vulgaris, hyperosteosis, and aseptic osteitis it is called the SAPHO syndrome (Hayem et al. 1999). In this thesis, SAPHO syndrome and/or arthritis associated with PPP is regarded as a type of PsA. Thus, PsA is a disease with many faces, and different clinical subtypes have been discussed. Originally, Moll and Wright proposed five different subtypes of PsA (Moll and Wright 1973): arthritis of distal interphalangeal joints with nail changes, spondylitis with or without peripheral arthritis, asymmetric monoarthritis or oligoarthritis, symmetric polyarthritis, and arthritis mutilans. However, longitudinal and thorough cross-sectional studies have questioned this strict subclassification of PsA, because some of the phenotypes described might co-exist, ie about a third of all PsA patients have been reported to have inflammatory back pain or spondylitis (Helliwell et

al. 1991). Also the subtype of peripheral arthritis might change during the disease course. A more pragmatic approach with therapeutic application would be to classify the patient as having axial joint involvement, peripheral arthritis or a combination thereof.

Nonetheless, stringent clinical and basic research into PsA requires the study of relatively homogeneous patient samples, and naturally consensus on how best to define PsA is needed. In august 2006 the international ClASsification of Psoriatic ARthritis (CASPAR) study group published data from a large prospective clinical and radiological classification trial, hoping this would bring consensus on the classification of PsA (Taylor et al. 2006). The CASPAR criteria found as a result of the study are presented in table 3.

Although, the CASPAR criteria might seem appealing they have several obvious limitations. First of

Table 3 summarizes the CASPAR criteria. One major criterion and at least a score of three points are needed to fulfill the classification criteria (modified from Taylor et al 2006).

Inflammatory arthritis (arthritis, clinical spondylitis, enthesophaty)	Major
Psoriasis (present, previous, or by family history)	2 points = present, otherwise 1 point
Seronegativity	1 point
Psoriatic nail dystrophy (present)	1 point
Juxta articular bone formation (hand/foot)	1 point
Dactylitis (present, previous by rheumatologist)	1 point

all, the study enrolled consecutive patients at different rheumatologic clinics, and therefore the control group was dominated by patients with RA making the criteria discriminative towards this diagnosis, whereas the number of patients with other types of spondarthritis was rather small. The latter group of patients often poses difficulties in differentiation between subtypes including PsA, which will not be solved by the CASPAR criteria. Furthermore, the CASPAR criteria also require the mandatory presence of arthritis, spondylitis and/or enthesitis, without further specification. Because enthesitis is a loosely defined clinical finding, introducing this in the classification criteria can be confusing. The same can to some extent be claimed for spondylitis. Nevertheless, the CASPAR study has received international support and only the future will show if these criteria will provide the way forward in the classification of PsA. Most studies currently still use the original Moll and Wright definition from 1973, and interestingly this first set of classification criteria performs well according to specificity and sensitivity compared to other established criteria (see table 4).

Table 4 presents sensitivity and specificity data from the CASPAR trial comparing different sets of classification criteria (modified from Taylor et al. 2006).

Criteria	Sensitivity	Specificity
CASPAR – Taylor et al. 2006	91	99
McGonagle et al. 1999	98	91
ESSG – Dougados et al. 1991	74	91
Vasey & Espinoza 1984	97	96
Moll & Wright 1973	91	98

Assessment of disease activity and function

Until recently, there has been little focus on clinical assessment methodology in PsA, and accordingly no consensus exists in this area. Consequently, clinical trials and long term clinical registries have used disparate outcome measures. However, due to emerging effective anti-TNF therapies, the focus on the methodology of outcome assessment has increased to ensure that standardized discriminate and responsive instruments are used. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) in conjunction with OMERACT has defined the following key domains to assess in PsA: joints, skin, enthesitis, dactylitis, spine, radiological joint damage, quality of life, and function (Mease et al. 2005a). These domains can be assessed by individual and/or combined measures. Some of these measures have been inherited from RA, ankylosing spondylitis, and psoriasis and adapted to PsA. Although the different measures have been shown to perform well in distinguishing placebo from treatment response, few have been validated in PsA.

Assessment of peripheral disease includes improvement in the ACR criteria, the EULAR response criteria, and the PsARC (psoriatic arthritis response criteria). They are all considered composite responder indices and have proved effective in discriminating between placebo and treatment response. ACR and EULAR criteria have been borrowed from RA (see previous description) while a response according to PsARC is defined as improvement in at least 2 measures (1 joint index measure + 1 global assessment measure) without worsening in any of 4 measures (Mease et al. 2000, Clegg et al. 1996). Remarkably the ACR and especially the EULAR criteria have recently been shown to be superior to the PsARC in PsA (Fransen et al. 2006).

Inflammation of the spine during the course of PsA poses greater difficulties in clinical trials (Mease et al. 2005a). First of all, spinal manifestations in PsA occurs less frequently (about one third of the patients) and with greater heterogeneity of expression than is seen in ankylosing spondylitis. Moreover, in older patients it is often difficult to distinguish inflammatory pain from the presence of degenerative disease, although imaging might be of some value. Thus, spinal inflammation has not been investigated in the reported studies of anti-TNF treatment in PsA (Mease et al. 2000, Mease et al. 2005b, Antoni et al. 2005). The ASessment in Ankylosing Spondylitis (ASAS) working group has recommended the use of a number of outcome measures for spinal involvement in ankylosing spondylitis, which includes the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (Garrett et al. 1994), the Bath Ankylosing Spondylitis Function Index (BASFI) (Calin et al. 1994) and the Bath Ankylosing Spondylitis Metrology Index (BASMI) (Jenkinson et al. 1994). The ASAS group has also developed a responder index: ASAS 20 and 40, based on elements of the above indices and other patient assessment scales for use in ankylosing spondylitis trials. However, further research is needed to clarify whether these instruments will perform well in PsA. In fact, when PsA patients with and without spinal disease were assessed in a clinic cohort, the BASDAI scores did not differ (Brockbank et al. 2001). Additionally, a cohort study of PsA patients showed that the BASDAI correlated more with self rated health than with disease activity in itself, while the Dougados Articular Index (Dougados et al. 1988) showed the contrary, suggesting that this index should be further investigated as a measure of spine inflammation in PsA (Taylor and Harrison 2004).

Although the above response measures provide acceptable assessment of peripheral and axial joint disease in PsA, they do not incorporate a full set of core domains to be assessed. Thus, important aspects of PsA are lacking, such as degree of skin disease, dactylitis, and entheseal involvement. Individual rating scales or scoring systems of each of these domains has been used (Mander et al. 1987, Heuft-Dorenbosch et al. 2003, Mease et al. 2005a), however the development of a more comprehensive response measure that is both responsive and discriminative will be a challenge for the future. Meanwhile, single unifying core sets such as improvement in VAS pain and VAS global health might be used (paper V in this thesis).

As with RA, adherence to therapy can also be used as a unifying measure of tolerability and efficacy in observational studies. Furthermore, generic quality of life instruments can be used to

provide response data comparable across different diagnosis and for health economic purposes.

Pharmacological treatment of rheumatoid arthritis and psoriatic arthritis

Pharmacological treatment of chronic polyarthritis consists of symptomatic and disease modifying therapy. Symptomatic treatment is the use of drugs, such as analgesics, without effects on the spontaneous course of the disease. These treatments will not be discussed further in this thesis. On the other hand, disease modifying therapies slows or preferably withholds the natural progression of the underlying disease, and these therapies can be divided into conventional DMARD therapy and biological agents. Glucocorticoids were formerly regarded as symptomatic treatment but accumulating evidence has supported this drug as being disease modifying in RA (Da Silva et al. 2006, Hoes et al. 2007, Kirwan et al. 2007), and thus these agents have a special position. The following section will primarily focus on biological agents, and only briefly describe conventional disease modifying therapy and the use of glucocorticoids. A presentation of the current Swedish treatment recommendations of RA and PsA will end this section.

Conventional DMARD treatment

The use of conventional DMARD therapy has undergone dramatic changes during the last century. In the 1920s intramuscular gold was introduced, and since then DMARDs have been used for treatment of arthritis. Originally, the types of DMARDs used were quite toxic and therefore withheld until late in the disease course of disabling arthritis. However, over the two past decades the refined weekly use of methotrexate (MTX) has emerged, and MTX is now also prescribed early in the disease course. In fact, several studies have demonstrated that early and aggressive treatment with MTX improves long term outcomes in RA (van Dongen et al. 2007, Verstappen et al. 2007, Emery et al. 2002b). Apart from MTX, anti-malaria drugs and sulfasalazine are the most commonly used drugs for RA treatment. Other DMARDs do exist but will not be discussed further in this thesis due to the limited usage in Scandinavia.

In PsA, the evidence demonstrating efficacy of therapy with traditional DMARDs is very limited (Jones et al. 2000). Methotrexate and cyclosporine are effective for treating the psoriatic skin manifestations, but support for improvement of the arthropathy is sparse (Jones et al. 2000, Nash and Clegg 2005). Based on available evidence and safety profiles MTX should be preferred over cyclosporine for the treatment of PsA (Jones et al. 2000) although at present this has not been systematically studied. In addition, there are some data that demonstrate marginal efficacy of sulfasalazine and perhaps gold in the treatment of peripheral arthropathy associated with psoriasis (Nash and Clegg 2005). Finally, neither of the traditional DMARDs have been shown significant impact on axial disease, dactylitis, or enthesitis. Moreover, evidence for prevention of radiological progression is lacking (Nash and Clegg 2005).

Unlike patients with PsA there is evidence that DMARD combination treatment is more effective than monotherapy in patients with RA (O´Dell et al. 2002, Boers et al. 1997, Möttönen et al. 1999). The COBRA study (Boers et al. 1997) demonstrated the efficacy of the step-down approach in suppression of inflammation and radiological progression. In addition, patients on combination treatment showed sustained long-term suppression of joint damage regardless of subsequent treatment (Landewe et al. 2002) indicating a window of opportunity during the early course of RA. The above studies showed advantages of different combinations of the most commonly used DMARDs in RA: methotrexate, sulfasalazine and hydroxychloroquine. On the other hand, the combination of MTX and Cyclosporine failed to show substantial clinical benefits in the CIMESTRA study (Hetland et al. 2006). Finally, it

should be noted that the patients in the combination studies often received fairly high doses of glucocorticoids. This makes interpretations of these studies somewhat difficult, especially in the light of the emerging evidence that glucocorticoids may be disease modifying.

Glucocorticoids

Glucocorticoids are effective anti-inflammatory agents widely used for treatment of arthritis. Previously, steroids were regarded as important symptomatic treatment of chronic arthritis, but with a severe and wide spectrum of toxicities limiting their usage in the longer perspective. However, recent studies have demonstrated a disease modifying potential of glucocorticoids in RA (Kirwan 1995, Landewe et al. 2002, Svensson et al. 2005, Kirwan et al. 2007). In addition, the evidence from low dose regimens seems to significantly reduce the level of toxicity with these agents, and thus change the risk/benefit ratio of glucocorticoids in favour of clinical usage in early RA.

With regard to the use of systemic glucocorticoids in PsA there are no available evidence. Therefore, systemic steroids should in general be used with caution because of the risk of provoking a pustular flare in the skin disease on withdrawal (Nash and Clegg 2005). Furthermore, there are no studies showing benefit of glucocorticoids for axial disease (Zochling et al. 2006). On the other hand, in PsA and RA periodic intra-articular injection of glucocorticoids can be of particular value in the management of patients with oligoarticular flares or those with controlled polyarticular disease apart from one or two persistently actively inflamed joints (Maugars et al. 1992).

In summary, systemic glucocorticoids during the early course of RA can be used in low dosages and/or for short periods. In established RA and PsA, however, the evidence or lack thereof suggests that systemic use of glucocorticoids should be reserved for short-term use during flares of disease activity or as temporary therapy until the efficacy of a DMARD is established (Morrison and Capell 2006).

Biological therapy

Biological therapy refers to the use of medication that is customized to specifically target an immune or genetic factor mediating disease (Staren et al. 1989). Many of these factors, which are mainly cytokines, are directly involved in the immune system. Biological therapy has primarily been used for the management of cancer (Talpaz et al. 1987, Kalinski and Mapara 2006) and autoimmune diseases (Weinblatt et al. 1999). In the field of rheumatology, biological agents blocking the cytokine TNF alpha plays a dominating role at present. There are currently three different anti-TNF therapies commercially available (listed in alphabetical order): adalimumab, etanercept, and infliximab. Adalimumab and infliximab are recombinant antibodies either fully human or chimeric (murine and human), respectively, whereas etanercept is a recombinant human fusion protein between a soluble TNFα/TNFβ binding receptor and the Fc part of IgG1. Differences in pharmacokinetics and pharmacodynamics exist between the anti-TNF therapies (El-Miedany 2004). These differences are summarized in table 5. Nonetheless, substantial evidence supports equal efficacy in RA (Hochberg et al. 2003, Chen et al. 2006, Kristensen et al. 2007). Moreover, combination therapy with all the TNF antagonists and MTX has proven more effective both for relieving symptoms and for retarding joint damage than monotherapy in RA (Lipsky et al. 2000, Klareskog et al. 2004, Keystone et al. 2004b).

In PsA, the anti-TNF agents have also been shown to be effective on signs and symptoms of the joint as well as the skin disease (Furst et al. 2007, Mease et al. 2000). As for RA even retardation of structural damage evidenced by conventional x-ray has been proven (Furst et al. 2007). On the other hand, concomitant MTX treatment has failed to improve response to anti-TNF agents in PsA trials (Antoni et al. 2005, Mease et al. 2005b).

Table 5 summarizes differences between the three commercially available anti-TNF agents in 2007 (modified from El-Miedany 2004).

	Adalimumab	Etanercept	Infliximab
Structure	Fully human antibody	Fully human fusion protein	Partly human and partly murine antibody
Half life	12–14 days	2–3 days	8–12 days
Route of administration	Subcutaneously	Subcutaneously	IV infusion
Soluble TNF alpha binding	High affinity, can form large complexes	Intermediate affinity, binds 1:1	High affinity, can form large complexes
Binding specificity	High specificity for TNF alpha	Binds both TNF alpha and TNF beta (Lymphotoxin)	High specificity for TNF alpha
Impact of cellular membrane TNF alpha binding	Can induce apoptosis	Binds to membrane bound TNF alpha without inducing apoptosis	Can induce apoptosis

In addition to anti-TNF agents other biological agents have emerged in the armamentarium of drugs used in chronic arthritis treatment. For patients with RA rituximab, a chimeric monoclonal antibody against CD20 specific B-cell antigen, has been approved (Edwards et al. 2004). Additionally, abatacept, a fusion protein of CTLA4, a molecule important for T-cell antigen presentation, and the Fc component of IgG1, has recently been approved (Kremer et al. 2003). Anakinra, a recombinant interleukin-1 receptor antagonist, is another principle tested for treatment of RA (Cohen et al. 2004). Finally, tocilizumab, a humanized anti-IL-6 antibody that inhibits the binding of IL-6 to the IL-6 receptor, has proven effective in larger trials of RA (Nishimoto et al. 2004), and is expected to be commercially available soon.

An exploratory trial of anakinra in PsA failed to demonstrate positive clinical results (Furst et al 2007). Apart from anakinra; rituximab, abatacept, and tocilizumab have not been systematically tested in PsA. However, alefacept, a fusion protein of LFA3, a molecule important for memory T-cell activation, and the Fc component of IgG1, used for psoriatic skin disease has shown improvements in joint signs and symptoms of PsA (Kraan et al. 2002). The exact role of this drug in conjunction with the other previously mentioned non-TNF blocking biologicals remains to be elucidated.

Treatment recommendations

In Southern Sweden, the CARISS group (Chronic Arthritis Research In Southern Sweden) has recently presented new treatment recommendations for RA. These recommendations represent an updated version of the Swedish national treatment guidelines from 2004 (www.srfonline.org). New national recommendations are expected to be launched in 2008 and will naturally substitute the temporary CARISS recommendations. MTX is now considered the first-line DMARD agent of choice for patients with RA, and early treatment initiation is important. Patients failing initial MTX treatment with high activity and/or discouraging prognostic factors may proceed directly to anti-TNF therapy. For patients failing MTX with lower activity and more favourable prognosis combination therapy with either sulphasalazine and/or hydroxychloroquine should be tested before proceeding to anti-TNF

treatment. If the patients fail the first treatment course of anti-TNF therapy he or she may switch to another anti-TNF drug. Subsequent failure to anti-TNF therapy should endorse switch to newer biological therapies such as abatacept or rituximab. Figure 1 summarizes the CARISS treatment recommendations.

The Swedish Society of Rheumatology has issued recommendations regarding PsA treatment. According to these, NSAIDs and glucocorticoid injections remain an important initial intervention.

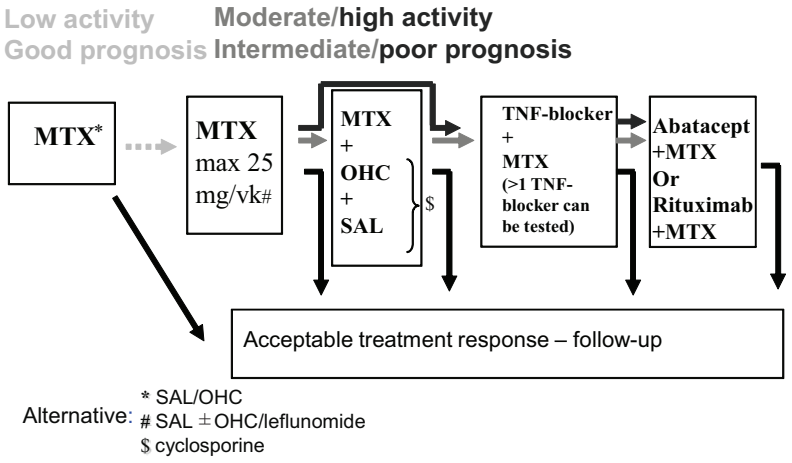

Figure1 presents RA treatment recommendations released by CARISS in June 2007. SAL = sulfasalazine; OHC = hydroxychloroquine; MTX = methotrexate.

Failure to these treatment attempts then results in two different scenarios. First, patients with active inflammatory axial disease only should proceed directly to anti-TNF therapy. Second, if the patient has a peripheral component either isolated or in conjunction with axial disease at least two conventional DMARDs should be tested. Sulfasalazine and methotrexate are the two preparations most commonly used, but treatment trials with cyclosporine or leflunomide are also within the recommendations. A summary of the guidelines for treating PsA is presented in table 6. If a patient fails the first anti-TNF treatment course preliminary evidence support switching to a different anti-TNF preparation (Furst et al. 2007).

Table 6 shows the Swedish Society for Rheumatology current recommendations for treatment and assessment of psoriatic arthritis (adapted from Swedish Society for Rheumatology 2005 - www.srfonline.org).

	1st line treatment		2nd line treatment	3rd line treatment
Psoriatic arthritis	NSAID and corticosteroid injections	Axial disease →	TNF antagonists (±MTX)	
		Peripheral disease →	MTX/ sulfasalazine/ cyclosporine/leflunomide	→ TNF antagonists (± MTX)

Observational studies and randomized controlled trials

Observational studies comprise research on subjects in a non-randomized setting with several possible research designs and many topics. The three most common study designs used in observational research are: cohort, case-control, and cross-sectional studies. However, many other types of observational analytic designs exist, such as nested case-control study, case series, and case reports. These will not be discussed further in this thesis.

Many important questions in medical research are investigated in observational studies (Glasziou et al. 2004). In fact, the vast majority of published medical research relies on data obtained from observational studies (Vandenbroucke et al. 2007a, b, and c). This has been acknowledged by the increasing interest, focus, and acceptance of these types of studies. Although observational studies do have obvious weaknesses in the study design (see below) it seems that the medical research paradigm has changed during the past few years. Focus has shifted from the downsides of observational studies to recognizing that they are important complements to randomized controlled clinical trials (RCT).

Strengths and weaknesses

The open non-randomized nature of observational studies imposes limitations of evidence because of potential bias and placebo effects. These factors are almost eliminated in the RCT setting. In fact, RCT is the only study design that controls for unknown and/or unmeasured confounders as well as those that are known and measured. Such confounders can distort the apparent effects of the intervention of interest. If this is the case, and the factor is dependent on the human interference it is called bias. Although, one can adjust for confounders or bias that are known and measured in observational studies, it is not possible to adjust for those factors that are not known to be confounders or that were not measured. Moreover, it can rarely be assumed that all important factors relevant to prognosis and response to treatment are known, and for those that are known difficulties may arise in accounting for them in analyses (Kunz and Oxman 1995). Four main types of bias may exist in cohort or case-control studies: selection, performance, attrition, and detection bias (www.cochrane.org). Selection bias arises from systematic differences in allocation to the groups that are compared. Differences in the care that is provided or exposure to other factors apart from the intervention is called performance bias, whereas differences in thresholds for withdrawals or exclusions of subjects in the different study groups are called attrition bias. Finally, detection bias refers to systematic differences in how outcomes are assessed. Bias can distort effects in either direction, causing them to appear either larger or smaller than they are. It is generally not possible to predict the magnitude, and often not even the direction of bias in specific studies (Kunz and Oxman 1995).

RCT characterized by randomization, double blinding, placebo controlling, and rigorous follow-up can prevent these types of biases. However, RCT cannot answer all important questions about a given intervention. RCTs are very costly compared to observational studies and therefore limited in the potential size of study population and duration of follow-up. Consequently, observational studies are more suitable to detect rare or late adverse effects as well as long-term efficacy of treatments. Furthermore, observational studies are not hampered by strict inclusion criteria and are more likely to provide an indication of what is actually achieved in daily medical practice (Papanikolaou et al. 2006, Pincus and Sokka 2004). Table 7 summarizes strengths and weaknesses of the cohort study design used in the current thesis compared to RCT. In the observational setting detection and performance bias can be reduced by blinding the evaluator or care giver, whereas selection bias can be avoided by randomization to the interventions investigated. Although these solutions seem attractive they are often impractical in the observational setting, where patient autonomy, care givers opinions and logistics play important and often compromising roles. On the other hand, bias in withdrawals or exclusion of subjects during the study (attrition bias) can be reduced by accounting for drug survival

or adherence to therapy when presenting response or effects to treatment at different follow-up times. In the RCT setting intention-to-treat analysis presents a feasible solution to attrition bias, however, this approach can not readily be applied in the observational setting. This matter will be discussed in detail later in this thesis (see section about the LUNDEX concept).

Finally, it should be stressed that research should be reported transparently so that readers can follow what was planned, done, found, and concluded. The reliability of research depends on a critical

Table 7 presents important differences between observational studies (cohort design) and RCT to be considered when planning or interpreting medical research.

Important research considerations	Observational studies (cohort design)	Randomized controlled clinical trials
Bias	Yes (selection, performance, attrition, and detection bias)	No, not within the study (but external bias may exist ie publication bias)
Placebo effect	Yes	No (not with double-blinded placebo control)
Time course	Long follow-up potential	Shorter study periods (usually < 1 year)
Study size	No upper limit	Predefined upper limits
Diversity of patients	Unlimited (represents clinical practice)	Limited by inclusion and exclusion criteria
Head-to-head comparisons	Possibility of head-to-head comparisons of products from different companies	Head-to-head comparison often unfeasible
Registration of side effects	Good with large study populations and long follow-up	Often limited to common side effects occurring without delay

assessment by others of the strengths and weaknesses in study design, conduct, and analysis. Transparent reporting is also needed to evaluate to what extent results can be included in systematic reviews (Jüni et al. 2001, Egger et al. 1998). Lack of transparency is often a problem in published observational research (Pocock et al. 2004), and there is a need for guidance in conducting and reporting observational studies (Rennie 2001, Vandenbroucke et al. 2007a). Therefore a network of statisticians, researchers, and journal editors was established to develop recommendations for the reporting of observational research. This network group has recently published: the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (Vandenbroucke et al. 2007a, b, and c). It is highly recommended that these guidelines are followed when reporting data from observational studies in the future. Also the guidelines can be an important inspiration when planning and conducting observational research.

Aims of the present investigation

The aims of this thesis were to study factors predicting efficacy and tolerability of tumour necrosis factor antagonists in patients with chronic arthritis. To accomplish this one main objective was to develop a new assessment method of drug efficacy suitable for long term observational studies. Specifically, the purposes were:

- to develop a new universal assessment method for drug efficacy in long term observational cohort studies of chronic diseases
- to apply this assessment method on anti-TNF treated RA and PsA patients
- to study predictors of drug adherence in RA
- to study predictors of drug adherence and serious adverse event rates in PsA
- to study predictors of response to anti-TNF antagonists in established RA
- to study response rates and predictors thereof in RA patients having failed their first treatment course of anti-TNF therapy

Protocol, study population, and methods

The SSATG database

All patients included in the studies of this thesis were monitored according to a standardized clinical protocol of the South Swedish Arthritis Treatment Group (SSATG) and registered in the SSATG database. The protocol was developed in 1999 at the Department of Rheumatology in Lund from previous nationwide protocols for early RA monitoring, but was modified and extended to make it more suitable for drug monitoring (Geborek and Saxne 2000). The inherent element of quality control in the protocol meets the legislative documentation required in Sweden, and therefore no formal approval from the ethical committee was necessary. After the introduction of the SSATG protocol the usage has expanded to 11 different centers of rheumatology in southern Sweden. The centers enrolling patients in the SSATG register cover a population of about 1.3 million. The protocol was designed to include and monitor all patients treated with biological agents regardless of rheumatic disease. Therefore variables central for drug monitoring including registration of adverse events are systematically recorded. Figure 2 illustrates the function and the flow of data sources in the SSATG register. A review of anti-TNF drugs sold in pharmacies compared to patients registered in our database revealed that about 90% of the patients receiving these drugs in southern Sweden were included in the database (Geborek et al. 2005b).

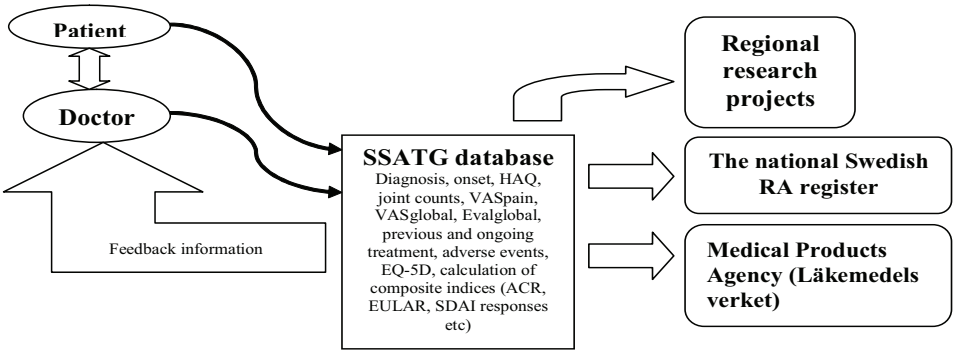

Figure 2 illustrates the functions and data sources of the South Swedish Arthritis Treatment Group (SSATG) register.

The computer database was developed in Microsoft Access® environment by Pierre Geborek, and central data entries were performed manually from paper forms recorded at the local centers constituting the SSATG collaboration. This centralization of data registrations ensured uniform registrations and minimized errors in the process of data transformation. The SSATG register is not only used for epidemiological research, but every 6 to 12 months feedback is given to the centers providing data. Thus rheumatologists can benchmark themselves according to prescribing standards in the entire SSATG. Moreover, the SSATG register also when appropriate transfers relevant data to the national Swedish drug surveillance authority (Medical Products agency) and the arthritis treatment database.

Study population

Paper I to IV

Patients, eligible for study I, II, III and IV had a diagnosis of RA according to clinical judgment by the treating physician. A review of a random subgroup (n=100) of these patients showed that 98 % of the patients fulfilled the American College of Rheumatology 1987 classification criteria for RA (Geborek et al 2002). Patients having received biologic therapy prior to inclusion were classified as switchers and excluded from study I, II, and III. Thus only patients receiving their first treatment course of biologic therapy (biologic naïve patients) were enrolled in these studies. Paper IV enrolled patients switching therapy.

Inclusion of patients started in March 1999. In paper I the patients were included until January 2004, the inclusion period for paper II lasted through December 2004, whereas patients in paper III and IV were included until December and September 2006, respectively. During the entire study period patients were continuously enrolled. Subjects eligible for TNF blocking therapy were selected by physicians based on disease activity and/or unacceptable steroid use. No formal level of disease activity was required. Nonetheless, the patients should have received at least 2 DMARDs including MTX previously without satisfactory response. Selection of a particular drug was primarily based on availability. In papers I and II only patients with infliximab and etanercept treatment were included. In paper III and IV patients with missing response data at 3 months of follow up were excluded. Baseline and other characteristics are presented in table 8.

Table 8 summarizes similarities and differences between the anti-TNF treated RA patients in study I to IV.

Characteristics	Paper I	Paper II	Paper III	Paper IV
Study size, patients	949	1161	1506	373
End of inclusion period	January 2004	December 2004	September 2006	December 2006
Mean age at inclusion, years	56	56	56	56
Females, %	78%	77%	77%	81%
Mean disease duration, years	14	14	12	14
Anti-TNF naive	Yes	Yes	Yes	No – includes switchers
Excluding patients if	Adalimumab treated	Adalimumab treated	Missing response data at 3 months	Missing response data at 3 months

The logistics in southern Sweden limited the usage of infliximab in 1999, while supply of etanercept was limited during the period February 2000 through June 2003 (figure 3). Treatment guidelines encouraged infliximab to be administered in combination with methotrexate. However, when infliximab was introduced in Sweden it was not obvious that co-medication with MTX was needed and that is why a substantial number of our infliximab patients were treated without concomitant MTX. Dosages of the TNF blocking agents followed the recommendations by the manufacturers. Etanercept 25 mg subcutaneously was administered twice a week. 40 mg of adalimumab was administered subcutaneously every other week. Infliximab was infused at 3 mg/kg at 0, 2, 6, and then every 8th week. Depending on primary or secondary failure the dosage of infliximab could be increased in steps of 100 mg to a maximum of 500 mg administered at 4 to 8 week intervals.

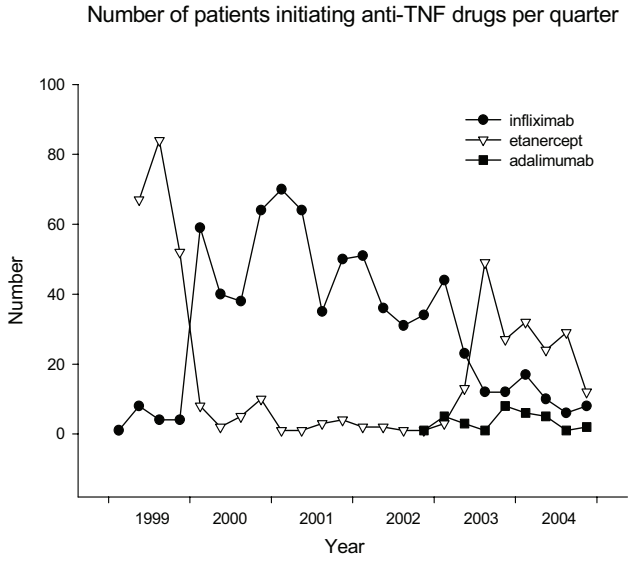

Figure 3 shows the number of RA patients per quarter starting infliximab, etanercept or adalimumab for the first time during the period 1999 through 2004 in southern Sweden.

Paper V

The 261 patients eligible for paper V had a diagnosis of PsA according to judgment of the treating physician. They were included from April 1999 thru September 2006. The subjects were selected for anti-TNF therapy based on high disease activity and/or unacceptable steroid use. Furthermore, the indication for TNF blocking therapy was supported by guidelines when such became available (www.srfonline.org). No predefined level of disease activity was required and no recommendation of type of anti-TNF agent was issued. However, as for the RA patients the access to the different anti-TNF therapies varied over the inclusion period (see figure 3). Only patients receiving their first treatment course of biologic therapy were enrolled in the present analysis. All anti-TNF therapies were administered as add on therapy, and no other DMARDs were added at treatment initiation.

Adalimumab was administered as a 40 mg subcutaneous dose every other week. Etanercept was administered twice a week with a 25 mg subcutaneous dosage. Infliximab was infused at 3 mg/kg at 0, 2, 6, and then every 8th week. Depending on efficacy the dosage of infliximab could be increased in steps of 100 mg to a maximum of 500 mg administered at 4 to 8 week intervals. The average dosage after 6 month was about 5 mg/kg every 8th week.

Methods

Clinical data were prospectively collected at 0, 3, 6, 12 months, and subsequently every 6-12 months. No patients were excluded due to lack of registrations at any particular follow-up time. Initially, and at each follow-up the following data were recorded: previous and concomitant DMARD treatment, systemic prednisolone dosage, Swedish version of Health Assessment Questionnaire (HAQ) score (Ekdahl et al. 1988), patient scored visual analogue scale for pain (VASpain) and general health (VASglobal), physician's global assessment of disease activity on a five grade Likert scale (Evalglobal), 28 tender and swollen joint count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

Any withdrawal from treatment was registered prospectively and classified by the treating physician as withdrawal caused by adverse events, lack of response/treatment failure, or miscellaneous. No criteria for inefficacy were predefined, and the decision relied upon the individual physician. The category "miscellaneous" mainly consisted of patients with poor compliance or subjects moving away from southern Sweden. In cases where cause of withdrawal was registered as both treatment failure and adverse event (AE), the reason of withdrawal was classified as an adverse event. For paper V, baseline characteristics also included overall pattern of joint distribution: spondylitis only, peripheral arthritis only, and combined spondylitis and peripheral arthritis. Arthritis in joints distal to the hip and shoulders were regarded as peripheral arthritis. Spondylitis was solely based on judgment from the treating physician. The registrations of overall joint distribution pattern were incomplete, and retrospective reviews of about 50% of the medical records were performed to complete this information.

For RA patients, improvement in the ACR response criteria of at least 20%, 50% and 70% (ACR20, ACR50 and ACR70 respectively) and the EULAR responses using 28 joint Disease Activity Score (DAS28) were calculated at given times of follow up. For PsA patients (paper V) EULAR responses based on 28 joint counts were chosen to assess clinical response because they have recently been validated and found more discriminative than the psoriatic arthritis response criteria (PsARC) in patients with peripheral arthritis (Fransen et al. 2006). Also, improvement in the VASpain and VASglobal of at least 50% (VASpain50 and VASglobal50, respectively) were calculated at given times of follow up, in order to detect response in patients with a component of clinical spondylitis. However, it should be stressed that no criteria for also assessing the spondylitis component of PsA have been validated.

All adverse events were prospectively collected by the treating physicians and classified according to the World Health Organisation adverse event terminology using forms from the Swedish Medical Products Agency. Also patients were independently urged to report adverse events by special forms systematically distributed to the patients prior to each follow-up. The final encoding and classification of adverse events were centralized and performed by a single responsible physician ensuring consistent reporting. Seriousness was graded as mild, moderate, or serious. Serious adverse events (SAE) were further divided into life threatening or lethal. Mild AE were self-limiting without any further treatment whereas moderate AE required medical treatment and/or professional observation. Generally, an adverse event resulting in hospitalization and in-hospital care was graded as SAE. However, if a patient was hospitalized for safety reasons and upon provocation did not develop any symptoms the event was graded as moderate. All malignancies were graded as SAE. AE occurring within 24 hours of an infusion were classified as an infusion reaction. Infusion reactions giving symptomatic dyspnoea and/or symptomatic drop in blood pressure were graded as serious, while those not provoking such symptoms were graded as moderate. All patients treated at the intensive care unit, undergoing large acute surgery, having immeasurable blood pressure or becoming unconscious were graded as having had a SAE. In this thesis data regarding SAE is only presented in paper V.

Statistics

Baseline clinical characteristics were analyzed by Kruskal-Wallis and Mann-Whitney U-test for comparison of groups for continuous variables, whereas Chi-square test was used for categorical variables. Values are reported as the mean ± SD except where stated otherwise. Adherence to therapy data were estimated according to Kaplan Meier and further analyzed with log-rank statistics for comparing different treatments. In paper I, IV, and V treatment responses were analyzed using Chi-square test, and in paper V Wilcoxon's paired rank test was used for studying changes in CRP-level compared to baseline. Cox proportional hazard models were used in paper II and V to investigate the effect of possible risk factors for treatment termination. These models were based on all patients included in the studies except where stated otherwise. Moreover, in paper II time-dependent Cox proportional hazard models were performed using covariates that might change over time (HAQ, CRP-level, and DAS28) to complement findings from the predictor analysis. Independent predictors of treatment response in paper III and IV were identified using a logistic regression model and association models. Subsequently, the predictors of EULAR and ACR response at 3 or 6 months were modeled using multivariate binary logistic regression models. The model assumptions for using the above mentioned regression analyses were tested and found valid. In paper V, adverse events were compared using Rate Ratios (RR) with 95% confidence interval. Level of significance was chosen to be $p<0.05$.

Results and discussion

The LUNDEX concept (Paper I)

Previously in this thesis bias when accounting for missing follow-up data in observational studies (attrition bias) have been described. In RCT this problem is solved by using intention to treat analysis with carry forward non-responder technique. However, in larger observational studies this type of analysis is inappropriate. Patients are continuously entering and exiting the study, and during the observational period some patients switch to different treatment groups within the study. Thus clinical information necessary for calculating response criteria for patients still receiving a certain therapy, and thereby remaining in the study, is sometimes missing. Thus using non-responder analysis on the intention to treat population will unfairly deflate response to therapy in larger observational settings where follow-up data are incomplete, because subjects with missing recordings of clinical response are accounted for as non-responders irrespective of their true clinical status.

On the other hand, only presenting available response data at certain times of follow-up uncritically inflates the apparent proportions of responses in clinical studies. Thus isolated use of either last observation carried forward (LOCF) or completer (per protocol) analyses does not yield information about the true fraction of patients actually responding to a particular therapy, since not all patients are adhering to the different therapies at certain times of follow up. Consequently, the per protocol (completer) response rates recorded in observational cohort studies reflect drug performances in selected groups of patients not accounting for differences in drop out among the treatment groups.

To meet these problems we developed LUNDEX (LUND Efficacy indeX), for measuring drug efficacy in larger observational cohort studies. LUNDEX provides a unifying concept of the fraction of patients adhering to therapy that truly achieves a specific response criterion after a defined follow up time. It is easy to utilize, and is calculated by multiplying the adherence to therapy proportion with the fraction of patients fulfilling a particular response criterion, as shown in figure 4.

LUNDEX = (Fraction of starters still in the study at time T) X (Fraction responding at time T)

Figure 4 presents the equation for LUNDEX.

In more mathematical terms, the LUNDEX is an index of the proportion (at a given time, T) of patients included (N_0), and remaining (N_T) on a particular therapeutic regimen with a corresponding adherence ratio (N_T/N_0), but also fulfilling certain response criteria (N_{RT}) with a corresponding success ratio (N_{RT}/N_{NRT}): $\text{LUNDEX}_T = [N_T/N_0] \times [N_{RT}/N_{NRT}]$. The different proportions of patients being studied at a given time T in a large observational cohort study with incomplete data recordings is illustrated in figure 5.

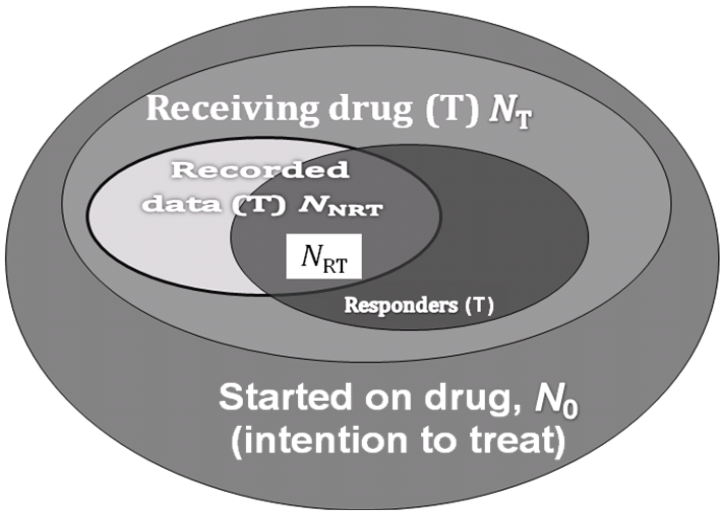

Figure 5 illustrates the different fractions of patients studied during an open label observational cohort study. N_0: patients included, T: a given time of follow-up, N_T: patients remaining on a particular therapeutic regimen at a given time of follow-up, N_{NRT}: patients with recorded response data at a given follow-up time, N_{RT}: with recorded response data AND fulfilling certain response criteria at a given follow-up time. N_T/N_0 = the adherence to therapy fraction. N_{RT}/N_{NRT} = per protocol response rate. $LUNDEX_T = [N_T/N_0] \times [N_{RT}/N_{NRT}]$.

Thus, LUNDEX can be applied without having to use intention to treat analysis, and in this way facilitate the process of evaluating therapies in clinical observational studies where patients are continuously initiating and stopping therapies. It should be stressed that an important assumption for using LUNDEX adjusted response rates is that the response data recorded are also representative for the patients with missing follow-up data but who are still remaining on therapy. When using LUNDEX adjusted response rates, measures should be performed to check for this assumption.

Interestingly, a recent study explained that if data are exhaustively recorded for all subjects at a given time-point non-responder analysis used in RCT settings and LUNDEX adjusted efficacy responses are equal. This suggests that LUNDEX is an unbiased measure in observational studies. Finally, the use of LUNDEX adjustment in observational trials not only presents statistical advantages, but it also increases the clinical transparency with the presentation of the true fraction of patients, who actually benefit from the intervention (Kristensen et al. 2007).

LUNDEX adjusted and per protocol response data in rheumatoid arthritis and psoriatic arthritis (Paper I and V)

For RA patients (Paper I) LUNDEX was calculated for the treatment groups at 12 and 36 months for the ACR50 and EULAR good responders. Data are presented in figure 6. For comparison the figure also includes the proportion responders at each follow up using the per protocol technique, i.e. the proportion responders of those actually evaluated. Also, response rates calculated by non-responder technique are displayed. During the first 12 months, etanercept had the highest overall LUNDEX values with nearly 35% and 28% of patients started on etanercept treatment fulfilling ACR50 and EULARgood response criteria, respectively. This fraction decreased to around 30% and 26%, respectively, after 3 years of follow up. On the other hand, around 28% and 25% of patients started on infliximab fulfilled ACR50 and EULAR good response criteria at 12 months, dropping to about 20% and 18% after 3 years of follow up.

For PsA patients (Paper V) LUNDEX were calculated for the treatment groups at 3, 6, and 12 months for the EULAR good and VASglobal50 responses (VASpain50 and EULARoverall see Paper V). Data are presented in figure 7. Generally, patients treated with concomitant MTX had a trend for higher LUNDEX values. The LUNDEX corrected response fractions all declined during the follow up period as a consequence of drop out during the observational period. Thus at 1 year of follow up, the

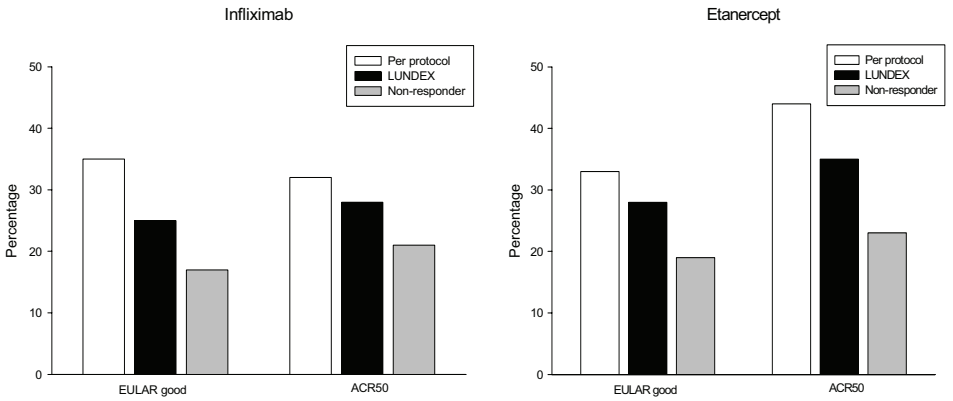

Figure 6 presents percentage of RA patients responding with either ACR50 or EULAR good response during anti-TNF treatment at 12 months grouped according to per protocol, LUNDEX, and non-responder analysis, respectively.

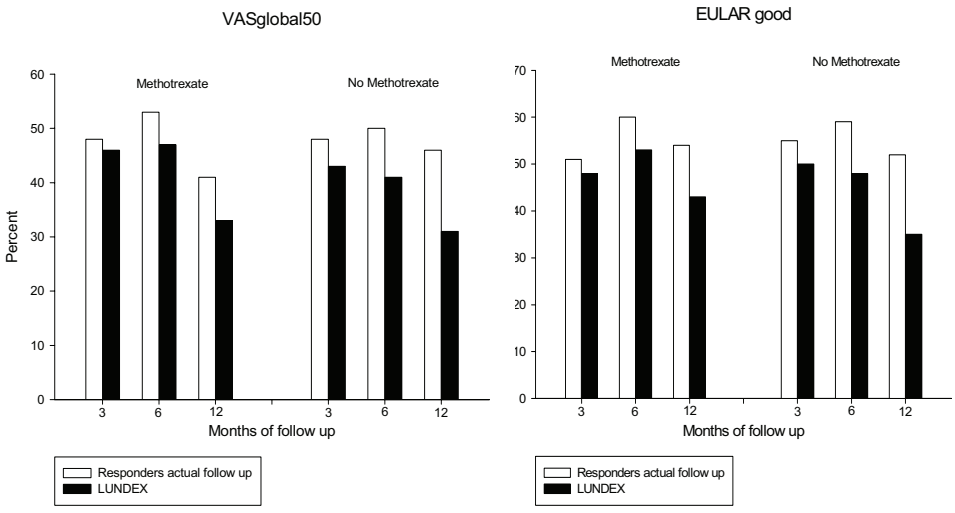

Figure 7 shows LUNDEX using VASglobal50 and EULARgood responders for PsA patients, grouped according to concurrent methotrexate usage at different times of follow up. Also the respective responder proportions are included as blank columns.

proportion of included patients with and without concurrent MTX actually responding according to the EULAR good criteria were 43% and 35%, respectively. The corresponding values for VASglobal50 were 33% and 31%, respectively.

The results described above from paper I and V presents LUNDEX as a suitable index for comparing biologic therapies in observational studies. As illustrated by figures 6 and 7 LUNDEX gives considerably lower values compared to the per protocol technique, and differences between treatments are seen. Conversely, LUNDEX adjusted responses are not deflating the response rates in an unjustified manner as would be the case when using non-responder analyses in a larger open study setting (see figure 6). Thus the use of LUNDEX in observational cohort studies with incomplete follow-up data provides a balanced method for minimizing attrition bias and provides transparent clinical information about the fraction of patients who actually experiences a true response at a given time of follow-up.

Drug adherence and predictors thereof in rheumatoid arthritis and psoriatic arthritis (Paper II and V)

Drug survival or adherence to therapy has been used in many open observational studies as a surrogate response measure for combined efficacy and tolerability of a given therapy studied. It also provides a quick and readily comparable measure (ie median drug survival time) allowing for direct and indirect treatment comparison.

Paper II and V in this thesis focused on this measure in RA and PsA patients, respectively. The primary objective of paper II was to compare head-to-head rates of drug survival of infliximab and etanercept, whereas other predictors of drug survival during anti-TNF therapy in RA were secondary end points. In paper V, the primary end point was to study impact of concomitant MTX treatment on anti-TNF drug survival rates. Secondary, other potential predictors such as gender, age, type of anti-TNF therapy were studied.

In order to control for selection bias or confounding and study predictors of drug survival Cox proportional hazard regression models were used in both studies.

Overall adherence to therapy in RA patients (paper II) for infliximab were generally lower than for etanercept ($p<0.001$). Adherence to therapy for etanercept and infliximab grouped according to concomitant DMARD usage are shown in figure 8. When studying termination because of adverse events only, patients treated with infliximab have more withdrawals because of adverse events when compared to etanercept ($p<0.001$). However, when studying withdrawals due to treatment failure the differences between infliximab and etanercept were less obvious and only significant for the subgroups of patients receiving MTX ($p=0.026$) and monotherapy ($p=0.002$). Thus termination due to adverse events mainly account for the differences seen in total adherence to therapy between etanercept and infliximab.

A Cox proportional hazard regression analysis was used to study other predictors of drug survival in RA and to control for possible confounders to the differences seen between infliximab and etanercept. Table 9 shows hazard ratios and 95% confidence intervals for the regression analysis. When adjusting for differences in baseline data, MTX was shown to protect against premature treatment termination when compared to other concomitant DMARDs and monotherapy. Also after adjustment, all patients treated with infliximab increased their risk of stopping therapy when compared to etanercept from 2.4 to nearly threefold. Furthermore, using HAQ, CRP-level, and DAS28 scores as time-dependent covariates showed similar findings with only minor decrements in differences described above (table 9). Independent of anti-TNF treatment and concomitant DMARD therapy, significant predictors of premature treatment termination were higher age (Hazard Ratio (HR)=1.11, CI:(1.01;1.22)), higher HAQ-score (HR=1.17, CI:(1.06;1.30)), and higher previous number of DMARDs

at inclusion (HR=1.13, CI:(1.02;1.25)). On the other hand, high CRP-level at treatment initiation was a predictor for prolonged drug adherence (HR=0.90, CI:(0.81;0.98)). Gender, year of treatment initiation, DAS28-level and disease duration prior to treatment initiation did not predict the level of adherence to therapy in anti-TNF treated RA patients.

Overall adherence to therapy for PsA patients (Paper V) treated with TNF blocking agents in combination with MTX were generally higher than for patients not receiving this combination (p=0.10). As can be seen in figure 9, drop outs because of adverse events primarily accounted for the differences seen (p<0.01).

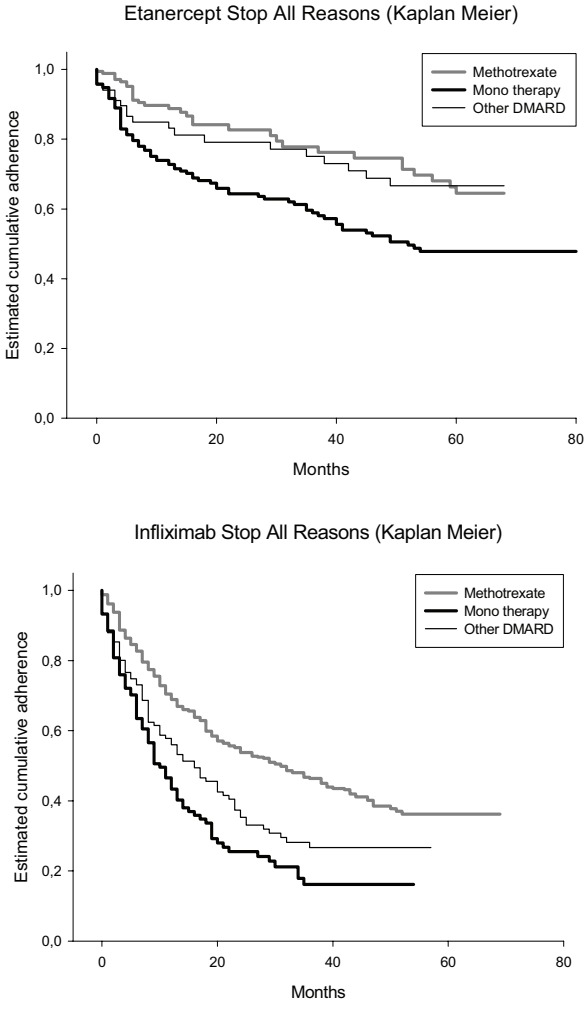

Figure 8 displays overall drug survival (as the fraction between 1 and 0) for patients treated with etanercept and infliximab split according to concomitant DMARD treatment.

Table 9 presents Hazard Ratios (HR) with 95% confidence intervals and level of significance for stopping treatment. The first row contains unadjusted data, while the remaining data were adjusted for differences in age, gender, year of treatment initiation, DAS28, HAQ, disease duration, previous DMARDs and CRP-level. Data presented in the second section uses HAQ, DAS28 scores and CRP levels as time dependent covariates. * Also adjusted for differences in concomitant DMARDs. ** Also adjusted for differences in TNF blocking treatment.

	HR (95% CI)	Level of significance
Unadjusted		
Infliximab vs Etanercept	2.37 (1.91; 2.93)	p<0.001
Adjusted		
*Infliximab vs etanercept	2.92 (2.32; 3.69)	p<0.001
**Monotherapy vs MTX	1.82 (1.45; 2.29)	p<0.001
**Other DMARD vs MTX	1.45 (1.12; 1.87)	p<0.010
**Monotherapy vs Other DMARD	1.22 (0.94; 1.61)	p=0.127
Adjusted with time-dependent Cox regression analysis		
*Infliximab vs etanercept	2.83 (2.27; 3.54)	p<0.001
**Monotherapy vs MTX	1.48 (1.19; 1.85)	p<0.001
**Other DMARD vs MTX	1.33 (1.08; 1.55)	p=0.017
**Monotherapy vs Other DMARD	1.10 (0.86; 1.40)	p=0.448

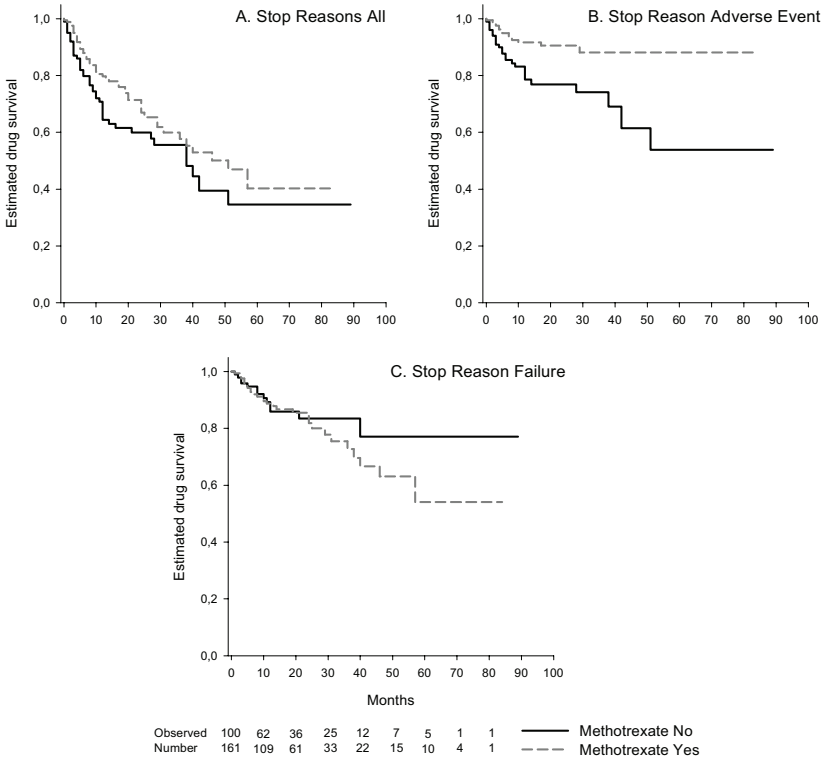

Figure 9 shows drug survival for psoriatic arthritis patients treated with anti-TNF therapies as the fraction (between 1 and 0) of patients remaining on therapy during the observation period. Withdrawal due to any reason (1A), adverse events (1B), or failure to treatment (1C) is presented separately. The number of patients under observation at each time point is listed below the figures.

To identify predictors for premature treatment termination and to evaluate whether potential baseline differences influenced adherence to therapy, a Cox proportional hazard regression analysis was performed. The regression analysis is presented in figure 10 with hazard ratios and 95% confidence intervals. When adjusting for different covariates, concomitant MTX protected significantly against premature treatment termination of TNF blockers in patients with PsA (p=0.03). Also, high CRP-level at treatment initiation in PsA patients was a predictor for prolonged drug adherence (p=0.03). Moreover, patients treated with etanercept had about half the risk of stopping therapy when compared to infliximab (p=0.01). Male sex, concomitant NSAID usage, pattern of joint distribution, previous number of DMARDs, and disease duration prior to treatment initiation did not predict the level of adherence to therapy. A subgroup regression analysis on termination reasons was performed. Accordingly, the protective association of concomitant MTX and etanercept appeared due to significantly fewer drop outs because of adverse events (p<0.01 and p=0.02, respectively).

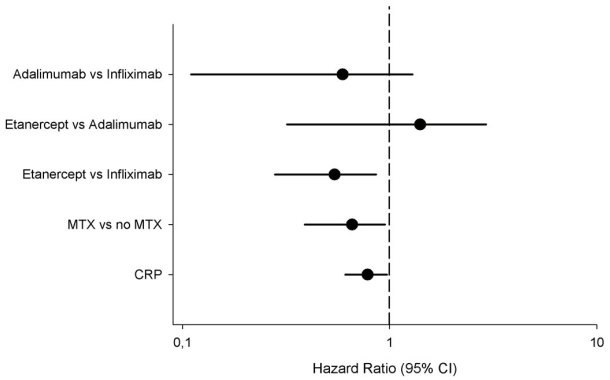

Figure 10 shows hazard ratios, 95% confidence intervals, and level of significance on a logarithmic scale for the predictors of treatment termination studied. Low hazard ratios indicate good drug adherence. The hazard ratio for CRP is given per SD increment of CRP concentration.

The results presented from paper II and V demonstrate an association between concomitant MTX usage and higher level of adherence to therapy with anti-TNF blockers. Also, high CRP level and etanercept treatment compared to infliximab were consistently associated with improved drug survival in RA as well as PsA. For RA patients, adjusting for potential confounding factors further accentuated the difference. Our study identifies withdrawal due to adverse events as the main cause of differences in total adherence to therapy between infliximab and etanercept. In addition, the positive impact of concomitant MTX was also primarily associated with fewer drop outs because of adverse events.

It should be stressed that reasons for ceasing treatment is registered by the treating physician, and inter-observer variation in classification of stop reason therefore exists. Thus results regarding cause of treatment termination must be interpreted with care, placing more emphasis on overall adherence to therapy. Although potential bias also exists when using this measure in drug studies, the wide use of this pragmatic surrogate measure for combined efficacy and tolerability makes it suitable for head-to-head and further inter-trial or indirect comparisons.

The improvement in adherence to therapy with concomitant MTX usage has been shown in other independent anti-TNF treated cohorts (Zink et al. 2005, Ostergaard et al. 2007). One reason underlying this difference could be that MTX effectively inhibits the formation of immunopathogenic antibodies

against anti-TNF products, thus decreasing the risk for adverse events (Baert et al. 2003, Cutolo et al. 2001). Another explanation could be that patients not receiving MTX also have uncharacterized co-morbidities predisposing to lower drug survival. Thus at the present stage the connection between concomitant MTX and improved drug survival remains an association without well established causality.

The finding that high CRP-level at inclusion seems to protect against treatment termination is probably because patients with a high level of systemic inflammation have a larger potential for improvement during therapy.

The finding that etanercept when compared to infliximab is associated with increased drug survival is the most controversial finding and should be interpreted with caution. Confounding by indication and varying access of different TNF blocking drugs during the inclusion time from 1999 through September 2006 (figure 2) makes the findings less solid at present. However, in RA patients adjustment for confounders increased the Hazard Ratio for terminating treatment of infliximab compared to etanercept from 2.37 to 2.92 (table 9), indicating that potential selection bias might have favoured prescription of infliximab over etanercept. Also, consistent findings have been reported from independent treatment cohorts (Ostergaard et al. 2007, Gomez-Reino et al. 2006). This together with the magnitude of the differences found increases the strengths of the evidence considerably (The GRADE working group 2004).

The open non-randomized nature of our observational cohort may induce bias in the process of selecting patients for particular treatments and the subsequent care and collection of data. Thus, further studies on TNF blocking drugs used in PsA and RA are needed to further validate the results, especially before making any definitive interpretations of causality between the positive effect on drug survival of MTX and etanercept.

Predictors of treatment response to anti-TNF therapy at 3 months in rheumatoid arthritis (Paper III)

After having studied predictors of drug survival in RA patients, we wanted to study predictors of drug response at 3 months of follow up. Clinical evaluation at three months represents a central assessment point regarding treatment continuation according to local and international recommendations. The predictors found therefore may help characterize patients with potential of a favourable response to anti-TNF treatment. Also 3 months of follow-up was chosen to ensure low number of dropouts due to incomplete data. As outcome variables we chose different response criteria (ACR and EULAR) to see whether choice of outcome measure influenced the results of the predictor analysis.

A multivariate binary logistic regression model was created for ACR50, ACR70, EULARgood, and EULAR remission (DAS < 2.6) to look for relevant predictors. Figure 11 show Odds Ratios (OR) and 95% confidence intervals for the predictors studied.

Concomitant MTX use was associated with favourable response according to all 4 criteria studied. Also, concurrent other DMARD treatment showed a trend for predicting good treatment responses with significant responses for EULAR good, DAS remission, and ACR50 response. HAQ score was inversely associated with response to TNF blocking therapy. High HAQ score reflects low functional level in RA patients, thus better functional capacity predicts good treatment response.

Disease activity at treatment initiation showed a dichotomized association with treatment response depending on response criteria chosen. Thus DAS28 scores were directly associated with favourable response when measured by ACR50 (OR: 1.59 $p<0.01$) and ACR70 (OR: 1.60 $p<0.01$), whereas disease activity was inversely associated with DAS28 remission (OR: 0.78 $p<0.01$) and EULAR good response, although the latter association was not significant ($p=0.09$). Disease duration did not predict treatment response.

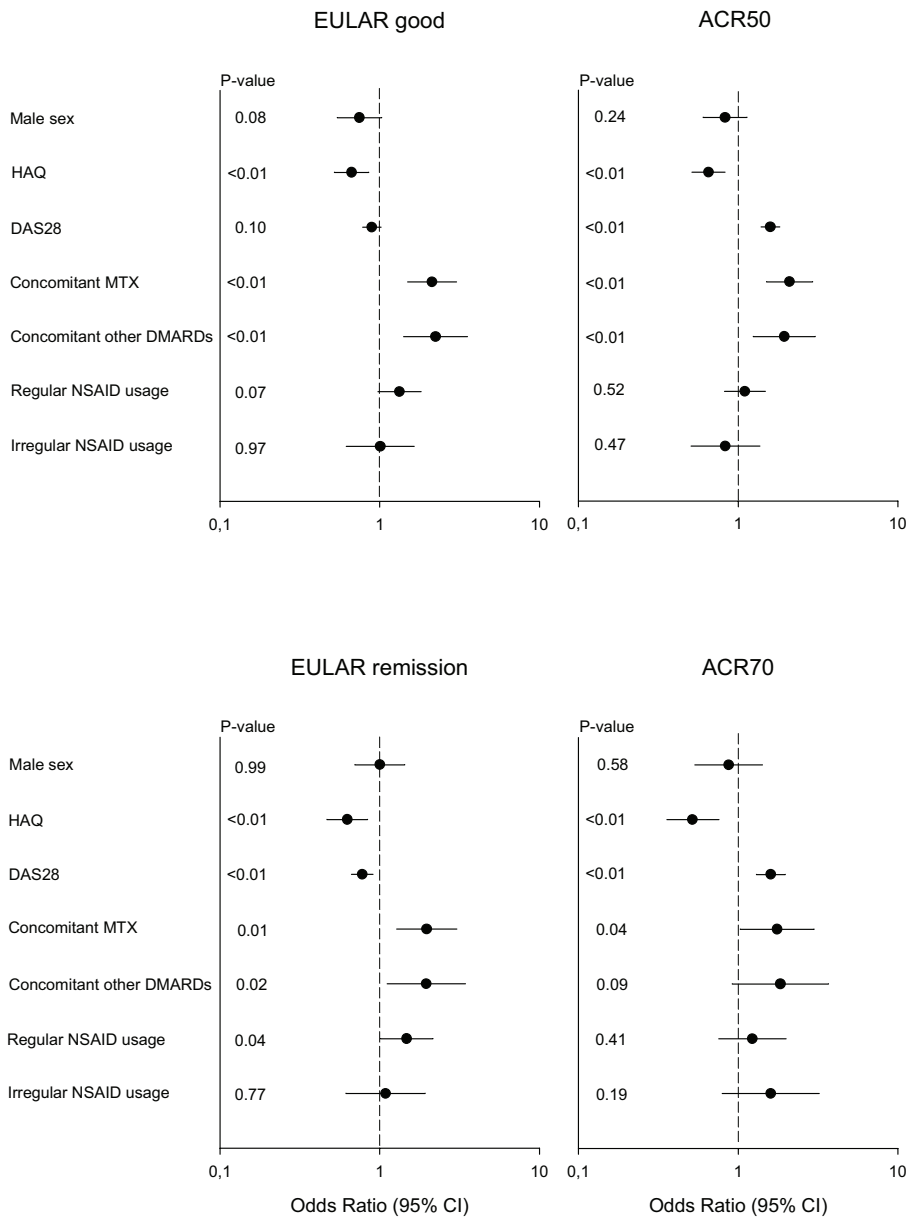

Figure 11. Odds ratios (OR), 95% confidence intervals (95% CI), and level of significance for predictors of EULAR good response (A), ACR50 response (B), ACR70 response (C), and remission (D) as measured by DAS28 less than 2.6 at 3 months of follow up.

We did not find any predictive value of gender for either of the 4 response criteria. Regular NSAID usage was a significant positive predictor of DAS28 remission (p=0.04).

Concomitant MTX usage and low HAQ score at treatment initiation was identified as predictors of good treatment response for all 4 response criteria studied. This is consistent with predictors of drug survival in RA (see previous section) and with the study reported by Hyrich et al 2006. Furthermore, concurrent treatment with other DMARDs identified good responders. In addition, we found a dichotomized relationship between disease activity at baseline as measured by DAS28 score, and response to either ACR criteria or EULAR criteria including remission DAS28<2.6. Thus depending on the response criteria chosen, DAS28 score was either directly associated with treatment response (ACR criteria) or inversely associated (EULAR criteria).

The direct association found between ACR50 and ACR70 responses and baseline DAS28 might be explained by a greater potential for treatment response in patients with high disease activity. This was not reproduced for predictors of EULAR good response possibly because of the inherent dependency of EULAR good responders to reach absolute DAS28 scores of less than 3.2 (van Riel et al 2000), much in analogy with the requirement for fulfilling the EULAR remission criteria (figure 1). On the other hand, ACR response criteria do not measure absolute disease activity, thus patients fulfilling the ACR50 criteria may still have rather high disease activity.

In contrast to previous reports (Hyrich et al. 2006, Forslind et al. 2007, Straube et al. 2006) of the association between male sex and favourable response to treatment in RA, we did not find any association between gender and response to anti-TNF treatment. In our study males generally had lower DAS28 scores both at baseline and at 3 months of follow up. Thus it can be speculated that the predictive value of male sex found by Hyrich et al is to some degree confounded by lower baseline scores of DAS28.

Response rates and predictors thereof in rheumatoid arthritis patients having failed their first treatment course of anti-TNF therapy (Paper IV)

In the previous section presenting drug survival during anti-TNF therapy in RA (paper II), it was clear that many patients stopped treatment either because of failure or adverse events. Many of these patients subsequently switch treatment to another type of anti-TNF blocking agent. Therefore the aims of Paper IV were to report response rates of first-time anti-TNF switchers (SW1) and second-time anti-TNF switchers (SW2) respectively, and to identify baseline predictors of response to a second anti-TNF treatment-course. SW2 were restricted to patients having previously failed one receptor and one antibody-type agent.

Response rates for SW1 and SW2 patients at three months are presented in table 10. Also included are response rates of SW1 grouped according to withdrawal-reason of the previous anti-TNF therapy (adverse events or inefficacy). ACR20 and ACR50 response criteria were met by 51% and 27% of SW1

Table 10 presents treatment response rates at three months for all first-time switchers, first-time switchers grouped according to previous withdrawal reason, and all second-time switchers. * = p<0.05 as compared to first-time switchers with previous adverse events.

Response criteria	1st time switchers n=337	1st withdrawal due to adverse events n=138	1st withdrawal due to inefficacy n=137	Second-time switchers n=36
ACR20 % (95% CI)	51 (45–56)	57 (48–65)	46 (38–55)	35 (18–52)
ACR50 % (95% CI)	27 (22–31)	32 (24–40)	21* (14–28)	18 (4–31)
EULAR good % (95% CI)	25 (21–30)	32 (24–40)	19* (12–26)	9 (0–19)
DAS28 remission % (95% CI)	16 (12–20)	19 (13–26)	12 (6–18)	6 (0–14)

respectively. For EULAR good and DAS28 remission (DAS28 <2.6), corresponding rates were 25% and 16%. Outcome rates of SW2 were clearly inferior to those of SW1. This was most apparent for the more stringent response-measures EULAR good (9% and 25%) and DAS28remission (6% and 16%). ACR50 and EULAR good response rates of SW1 having failed the former anti-TNF treatment due to adverse events were significantly better than those of patients having switched due to inefficacy. Likewise, significantly more patients in the group of patients switching because of previous adverse events had a low disease-activity (DAS28low) at three months. For comparison, three months per protocol response-rates of RA-patients receiving first TNF-inhibitor were: ACR20: 61%; ACR50: 37%; EULAR good: 34%. DAS28remission: 23%.

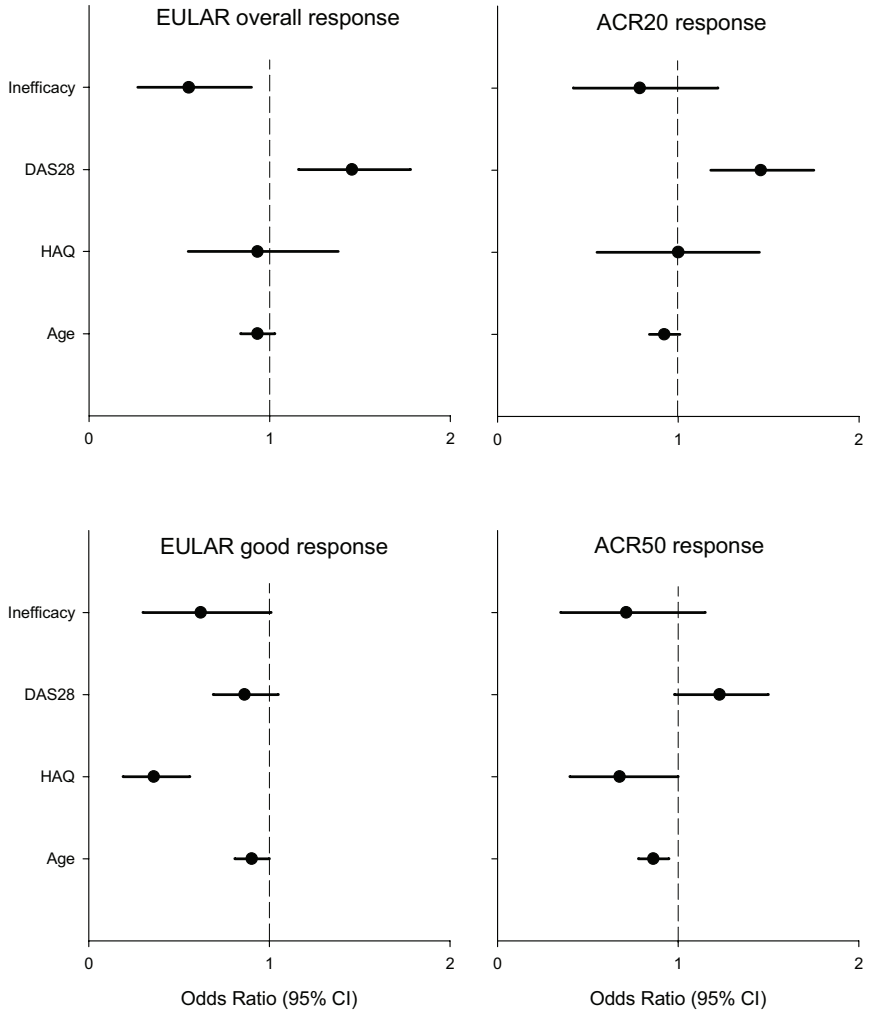

Figure 12. Odds ratios (OR) with 95% confidence intervals (95% CI) for predictors of EULAR overall, ACR20, EULAR good, and ACR50 responses at 3 months of follow up for 1st time anti-TNF switchers.

Predictive potentials of baseline age, HAQ- and DAS28-scores and were calculated using multivariate binary logistic regression models. Predictive potentials of having ceased the initial treatment due to inefficacy rather than adverse events were assessed in separate sub-analyses (n=261). Results are presented as odds ratios with 95% confidence intervals in figure 12. Lower baseline HAQ-scores were shown to predict ACR50 (OR 0.63 [95% CI 0.40-1.00]) and EULAR good (0.33 [0.19-0.56]) responses at three months, but not the less stringent outcome measures. Higher baseline DAS28-values were predictive of ACR20 (1.44 [1.19-1.75]) and EULAR overall (1.43 [1.16-1.78]) responses, while not reaching significance for ACR50 (1.21 [0.98-1.50]). By contrast, regarding EULAR good, the predictive value of a higher

DAS28, showed an opposite tendency (0.85 [0.69-1.05]). This is consistent with results from naïve anti-TNF treated RA patients (paper III). Lower age was identified to predict ACR50 response (0.86 [0.78-0.95]), and a similar trend was seen for the other outcome measures. Interestingly, concurrent MTX use was not shown to be clearly superior to anti-TNF monotherapy in any of the models. Sub-analyses (n=261), revealed patients to be less likely to achieve a EULAR overall (0.49 [0.27-0.90], p=0.021) and/or EULAR good-response (0.55 [CI 0.30-1.01], p=0.054), having ceased the first anti-TNF treatment because of inefficacy, rather than adverse events. The same trend was seen for ACR-criteria, although non-significant.

The response rates of SW1 presented in this study are similar, or at least not markedly inferior, to those previously reported regarding anti-TNF naives (Keystone et al. 2004a, Lipsky et al. 2000, Maini et al. 1999, Bathon et al. 2000, Weisman et al. 2003). In contrast, the current study shows response to a third anti-TNF treatment-course, following failures with one antibody- and one receptor-type agent, to be markedly lower than SW1. Identified baseline predictors of response for SW1 were lower age and HAQ-scores, higher DAS28-values and having ceased the first anti-TNF treatment due to adverse events rather than inefficacy. No variable, however, was significantly associated with all response-measures examined, thus limiting the external validity of the predictors found. Also the low number of subjects in the group of SW2 limits the evidence, and more studies are needed to confirm our findings. However, based on the available evidence it is fair to claim that switching to a second treatment course of anti-TNF is reasonable while patients withdrawing from their second trial of anti-TNF therapy should be offered other treatment options such as abatacept and rituximab.

Serious adverse events in anti-TNF treated psoriatic arthritis patients (Paper V)

Another important goal of paper V was to present data on serious adverse events, since long-term safety data are scarce in this growing category of anti-TNF treated PsA patients. The TNF blocking agents were generally well-tolerated during the observational period, with a similar and non-significant incidence of serious adverse events around 5-6% per year in patients treated with or without concomitant MTX (Table 11). Two malignancies were reported: a chronic lymphatic leukemia (CLL) in a patient without concomitant MTX, with possible subclinical debut prior to anti-TNF treatment, and a fatal non-Hodgkin lymphoma (diffuse large B-cell lymphoma) in a patient receiving concomitant MTX. Three life threatening adverse events were recorded, all in patients without concomitant MTX i.e. septicemia with E. coli bacteria, and two anaphylactic infusion reactions. All serious infusion reactions occurred during infliximab treatment. The serious infections mainly resided in the respiratory organs with no reported events of tuberculosis. The circulatory events consisted of one transient ischemic attack, two acute coronary syndromes, and two tachyarrhythmia's. The musculoskeletal adverse events consisted of three peripheral fractures and one cervical spinal stenosis requiring surgery. No rare or unexpected adverse events were reported during the treatment period.

The number of SAE seemed generally lower in this population of PsA (5-6%) compared to patients with RA (8-13%) treated in the same area and registered according to the same protocol (Geborek et al. 2002). This could possibly be explained by the difference in mean age of about 10 years between the two patient groups with RA patients being older (Geborek et al. 2002). The SAE rates are also somewhat lower than rates reported from RCTs (8-18%) on anti-TNF treated PsA with duration of more than 3 months (Antoni et al. 2005, Mease et al. 2005b). However, our data on adverse events mainly rely on a voluntary adverse event reporting systems, which tend to underestimate the true level of adverse events (Gartlehner et al. 2006), whereas adverse events reporting in the RCT setting are fare more rigorous.

Interestingly, we did not find one single case of tuberculosis in this PsA cohort with more than 500 observational years. This could be explained by the low incidence of tuberculosis in the background population of southern Sweden combined with the younger age of the PsA subjects compared to patients with RA where tuberculosis seems more frequent (Geborek et al. 2002). Finally, another important observation is that no unexpected types of SAE were reported.

Table 11 presents serious adverse events during the observational period graded according to WHO terminology. Exposure time, total rates and subtypes of adverse events are shown in the table.

	MTX	No MTX
Total treatment time (years)	319.5	209
Serious adverse events (SAE)	Number per 100 years of treatment	Number per 100 years of treatment
All SAE (number)	5.32 (17)	5.74 (12)
Infections	1.56 (5)	0.96 (2)
Circulatory events	0.94 (3)	0.96 (2)
Musculoskeletal	0.94 (3)	0.48 (1)
Malignancies	0.31 (1)	0.48 (1)
Infusion reactions	0.63 (2)	1.44 (3)
Other	0.94 (3)	1.44 (3)

Conclusions

Based on results obtained from the five studies included in this thesis the following conclusions can be drawn:

- A new universal assessment method called LUNDEX has been developed for measuring drug efficacy in long term observational cohort studies
- LUNDEX has been applied in anti-TNF treated RA and PsA cohorts showing balanced adjustments of response rates
- Treatment with etanercept rather than infliximab, concomitant MTX, and higher CRP-level at baseline were associated with improved adherence to anti-TNF therapy in RA and PsA
- Treatment with concomitant DMARDs, especially MTX, and low disability were associated with good response at 3 month of follow-up in RA. Choice of outcome measures influenced the predictive value of baseline features
- Response rates of first-time anti-TNF switchers are somewhat below those of anti-TNF naïve RA patients, while the response rates of second-time switchers are markedly inferior
- Lower age and HAQ scores, higher DAS28 values and having ceased the first anti-TNF treatment due to adverse events rather than inefficacy predicted good response to second-line anti-TNF therapy. None of the predictors for response to second anti-TNF treatment course were consistent for all outcome measures studied
- TNF blocking agents used in PsA were generally well tolerated with few serious adverse events and no unexpected ones

Perspectives for the future

The introduction of anti-TNF therapies has proved to be a major step forward in the treatment of chronic arthritis. Treatment with TNF blockers has been shown to be effective in reducing signs and symptoms of inflammation, but perhaps even more surprisingly they are significantly slowing development of tissue damage. Nonetheless, the long term consequences of these treatments are not fully known. Continuous surveillance of anti-TNF and other emerging biological agents in daily clinical practice is therefore important both for assessing treatment efficacy and to detect rare or unexpected side effects. The new assessment method, LUNDEX, was developed to undertake and refine the important task of monitoring drug efficacy in larger clinical observational cohorts. It is therefore hoped that LUNDEX will be used in future studies of drug efficacy in treatment of chronic arthritis. Moreover, the use of LUNDEX is universal for monitoring long-term treatment of other chronic diseases such as inflammatory bowel diseases, cardiovascular and neurological diseases, and so on. On the other hand, appropriate statistics for calculating accuracy of LUNDEX values found, including confidence intervals, needs to be developed.

This thesis has also reported the presence of predictors for treatment efficacy and drug survival in PsA and RA. However, many important research questions regarding use of anti-TNF treatments in clinical practice still need to be investigated:

- Studies of predictors of specific adverse reactions to anti-TNF agents
- Studies on long-term health economic issues
- Studies on dose escalation related to different diagnosis and other baseline characteristics
- Does any dose response relation exist for PsA and AS?
- Can anti-TNF therapies be used in patients with a previous history of malignancies?
- What is the impact of continuing or withholding therapy during surgery?
- What is the correlation between radiological impact and long-term efficacy of anti-TNF treatment?
- What is the role of anti-TNF treatment in pregnant and lactating women?
- Can anti-TNF treatment be discontinued after a period of satisfactory response?

Further research from observational registers and randomized controlled trials will hopefully answer many of these import questions.

Popularized summary in Swedish – Populärvetenskaplig sammanfattning

Reumatoid artrit (ledgångsreumatism/RA) och psoriasis artrit (PsA) är kroniska inflammatoriska sjukdomar där framför allt lederna är målorganet. Gemensamma symptom är också trötthet, smärta och nedsatt arbetsförmåga. Orsaken/er till dessa sjukdomar är fortfarande okända, men miljö och genetiska faktorer har identifierats. Tumörnekrotisk faktor (TNF) är ett signal protein som anses spela en viktig roll vid kroniska inflammatoriska ledsjukdomar och läkemedel som blockerar effekter av TNF (sk TNF-antagonister) har visat sig verksamma vid dessa sjukdomar. Man har sålunda i kliniska studier påvisat minskad ledsvullnad, ledömhet, och trötthet samt även bromsat utveckling av ledskador (destruktion) hos de flesta patienter med RA och PsA behandlade med TNF-antagonister.

Effektdata, som används i kliniska studier, är inte automatiskt applicerbara på de patientpopulationer som finns i klinisk praxis. I denna avhandling har vi därför studerat olika aspekter av behandling med TNF-antagonister (adalimumab, etanercept och infliximab) i den kliniska vardagen. Patienter i södra sjukvårdsregionen som får dessa behandlingar ingår sedan 1999 i en prospektiv observationell studie och informationen samlas fortlöpande i det så kallade SSATG registret (South Swedish Arthritis Treatment Group). Uppföljning enligt SSATG registret innebär regelbundna besök då patienter träffar en läkare. Vid dessa besök registreras antal svullna och ömma leder, eventuella biverkningar eller andra händelser som har inträffat och läkaren samt patienten själv gör en bedömning av sjukdomens aktivitet. Blodprover för kontroll av inflammation tas vid varje besök. Alla data registreras och skickas till Lund för central bearbetning. I första delarbetet har vi utvecklat ett alternativt mått som kombinerar behandlingseffekt (respons) och tolerabilitet, det så kallade LUNDEX (LUND Efficacy indeX). LUNDEX är produkten av fraktionen av patienter som uppnår respons vid tidpunkt T multiplicerat med fraktionen patienter som kvarstår på terapi vid tidpunkt T. LUNDEX är således den kliniskt relevanta fraktionen av patienter som svarar på en given behandling i en studiemiljö där man inte alltid har uppföljningsdata på alla patienter som fortfarande står kvar på behandlingen. Detta nya mått har använts i delarbete ett och fem på RA respektive PsA patienter.

I andra delarbetet har faktorer som kan förutsäga behandlingsavbrott med TNF-antagonisterna etanercept och infliximab vid RA studerats. Det har visat sig att behandling med metotrexat, vilket är det mest använda antireumatiska medlet vid RA, tillsammans med etanercept hos yngre patienter med hög systemisk inflammation (högt CRP) var den mest gynnsamma kombination om tidigt behandlingsavbrott skulle undvikas.

I tredje delarbetet har faktorer som kan förutsäga behandlingseffekt studerats vid RA. Vi har funnit att behandling med metotrexat, eller övriga antireumatiska medel och hög funktionsnivå hos patienterna ökade chansen att få en bra behandlingseffekt vid anti-TNF behandling.

I det fjärde arbetet studerades hur det gick för patienter som hade sviktat på första anti-TNF behandlingen. Resultaten visade att det var lönt med ett andra försök med TNF-antagonister, medan ett tredje behandlingsförsök hade betydligt sämre effekt.

Sammanfattningsvis har LUNDEX visats vara ett nytt värdefullt redskap för att evaluera kombinationen av tolerabilitet och behandlingseffekt såväl vid olika behandlingar som vid olika reumatiska sjukdomar i observationella studier. Viktiga faktorer som kan förutsäga behandlingseffekt och behandlingsavbrott har identifierats.

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References

Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol **2005**; 23 (Suppl 39): S100–108.

Antoni C, Kavanaugh A, KirkHam B, Tutuncu Z, Burmester GR, Schneider U et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum **2005**; 52:1227–1236.

Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum **1988**; 31:315–324.

Askling J, Fored CM, Baecklund E, Brandt L, Backlin C, Ekbom A et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis **2005a**; 64:1414–1420.

Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis **2005b**; 64:1421–1426.

Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. BMJ **1998**; 317:180–181.

Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum **2006**; 54:692–701.

Baert F, Noman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A. Influence of Immunogenicity on the Long-Term efficacy of Infliximab in Chron's disease. N Eng J Med **2003**; 348:601–608.

Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med **2000**; 343:1586–1593.

Bertinotti L, Nacci F, Matucci-Cerinic M. The measurement of outcome and the rheumatoid arthritis core set to lift the prejudice of the 'thaumaturgus'. Rheumatology **2006**; 45:1055–1057.

Boers M, Verhoeven AC, van der Linden S. [Combination therapy in early rheumatoid arthritis: the COBRA study]. Ned Tijdschr Geneeskd **1997**; 141:2428–2432.

Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trial. JAMA **2006**; 295:2275–2285.

Brockbank J, Schimmer J, Schentag C, Hyrich K, Gladman DD. Spinal disease assessment in psoriatic arthritis (PsA). J Rheumatol **2001**; 28 (suppl 63):62.

Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: Dimensions and Practical Applications. Health Qual Life Outcomes **2003a**; 1:20.

Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol **2003b**; 30:167–178.

Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol **1994**; 21:2281–2285.

Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark WW, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess **2006**; 10:1–248.

Clegg DO, Reda DJ, Mejias E, Cannon GW, Weisman MH, Taylor T et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. Arthritis Rheum **1996**; 39:2013–2020.

Cohen SB, Moreland LW, Cush JJ, Greenwald MW, Block S, Shergy WJ et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis **2004**; 63:1062–1068.

Cutolo M, Sulli A, Pizzorni C, Seriolo B, Straub RH. Anti-inflammatory mechanisms of methotrexate in rheumatoid arthritis. Ann Rheum Dis **2001**; 60:729–735.

Da Silva JAP, Jacobs JWG, Kirwan JR, Boers M, Saag KG, Inês LBS et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis **2006**; 65:285–293.

Dixon WG, Symmons DP. Does early rheumatoid arthritis exist? Best Pract Res Clin Rheumatol **2005**; 19:37–53.

Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum **2002**; 46:2287–2293.

Dougados M, Gueguen A, Nakache JP, Nguyen M, Mery C, Amor B. Evaluation of a functional index and an articular index in ankylosing spondylitis. J Rheumatol **1988**; 15:302–307.

Dougados M, van der LS, Juhlin R, Huitfeldt B, Amor B, Calin A et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum **1991**; 34:1218–1227.

Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med **2004**; 350:2572–2581.

Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. BMJ **1998**; 316:140–144.

Ekdahl C, Eberhardt K, Andersson SI, Svensson B. Assessing disability in patients with rheumatoid arthritis. Use of a Swedish version of the Stanford Health Assessment Questionnaire. Scand J Rheumatol **1988**; 17:263–271.

El-Miedany Y. Tumor necrosis factor alpha blockade in rheumatoid arthritis: responders vs non responders. Med Chem Reviews **2004**; 1:361–368.

Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS. Early referral recommendation for newly diagnosed rheumatoid arthritis, evidence based development of a clinical guide. Ann Rheum Dis **2002a**; 61:290–297.

Emery P. Evidence supporting the benefit of early intervention in rheumatoid arthritis. J Rheumatol **2002b**; 66 (Suppl):3–8.

Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum **1995**; 38:727–735.

Forslind K, Hafström I, Ahlmén M, Svensson B. Sex: a major predictor of remission in early rheumatoid arthritis? Ann Rheum Dis **2007**; 66:46–52.

Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, Van Riel PLCM. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: Analysis of data from randomized controlled trials of two tumour necrosis factor inhibitors. Ann Rheum Dis **2006**; 65:1373–1378.

Furst DE, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Sieper J et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007. Ann Rheum Dis **2007**; 66 (Suppl 3):2–22.

Gabriel SE, Crowson CS, O'Fallon WM. Comorbidity in arthritis. J Rheumatol **1999**; 26:2475–2479.

Gabriel SE, Crowson CS, Kremers HM, Doran MF, Turesson C, O'Fallon WM, Matteson E. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. Arthritis Rheum **2003**; 48:54–58.

Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol **1994**; 21:2286–2291.

Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. The Comparative Efficacy and Safety of Biologics for the Treatment of Rheumatoid Arthritis: A Systematic Review and Metaanalysis. J Rheumatol **2006**; 33:2398–2408.

Geborek P, Saxne T. Clinical protocol for monitoring of targeted therapies in rheumatoid arthritis. Rheumatology (Oxford) **2000**; 39:1159–1161.

Geborek P, Crnkic M, Petersson IF, Saxne T. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. Ann Rheum Dis **2002**; 61:793–798.

Geborek P, Bladström A, Turesson C, Gülfe A, Petersson IF, Saxne T et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis **2005a**; 64:699–703.

Geborek P, Nitelius E, Noltorp S, Petri H, Jacobsson L, Larsson L, Saxne T, Leden I. Population based studies of biologic anti-rheumatic drug use in southern Sweden. Comparison with pharmaceutical sales. Ann Rheum Dis **2005b**; 64:1805–1807.

Gladman D. Psoriatic arthritis. Baillière's Clin Rheumatol **1995**; 9:319–329.

Gladman D, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis **2005**; 64 (Suppl 2):14–17.

Glasziou P, Vandenbroucke JP, Chalmers I. Assessing the quality of research. BMJ **2004**; 328: 39–41.

Gomez-Reino JJ, Carmona L, and the BIOBADASER Group. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. Arthritis Res Ther **2006**; 8:R29.

Gülfe A, Geborek P, Saxne T. Response criteria for rheumatoid arthritis in clinical practice: how useful are they? Ann Rheum Dis **2005**; 64:1186–1189.

Hayem G, Bouchaud-Chabot A, Benali K, Roux S, Palazzo E, Silbermann-Hoffman O et al. SAPHO syndrome: A long-term follow-up study of 120 cases. Semin Arthritis Rheum **1999**; 29: 159–171.

Helliwell PS, Taylor WJ. Classification and diagnostic criteria for psoriatic arthritis. Ann Rheum Dis **2005**; 64 (Suppl 2):3–8.

Helliwell P, Marchesoni A, Peters M, Barker M, Wright V. A re-evaluation of the osteoarticular manifestations of psoriasis. Br J Rheumatol **1991**; 30:339–345.

Hetland ML, Stengaard-Pedersen K, Junker P, Lottenburger T, Ellingsen TJ, Andersen LS et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis Rheum **2006**; 54:1401–1409.

Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewe R, van ver Tempel H, Mielants H et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis **2003**; 62:127–132.

Hirsch R, Lin JP, Scott WW, Jr., Ma LD, Pillemer SR, Kastner DL et al. Rheumatoid arthritis in the Pima Indians: the intersection of epidemiologic, demographic, and genealogic data. Arthritis Rheum **1998**; 41:1464–1469.

Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumor necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis **2003**; 62 (Suppl II): ii13–16.

Hoes JN, Jacobs JWG, Boers M, Boumpas D, Buttgereit F, Caeyers N et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis **2007**; 66:1560–1567.

Hyrich KL, Watson KD, Silman AJ, Symmons DPM, and The BSR biologics Register. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology **2006**; 45:1558–1565.

Jacobsson LT, Hanson RL, Knowler WC, Pillemer S, Pettitt DJ, McCance DR et al. Decreasing incidence and prevalence of rheumatoid arthritis in Pima Indians over a twenty-five-year period. Arthritis Rheum **1994**; 37:1158–1165.

Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol **1994**; 21:1694–1698.

Jones G, Crotty M, Brooks P. Interventions for treating psoriatic arthritis (Cochrane Review). The Cochrane database of Systematic Reviews **2000**; 3. Art. No.: CD000212. DOI:10.1002/14651858. CD000212.

Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. BMJ **2001**; 323:42–46.

Kalinski P, Mapara M. 9th Annual Meeting of the Regional Cancer Consortium for the Biological Therapy of Cancer. 16-18 February 2006, UPMC Herberman Conference Center, Pittsburgh, PA, USA. Expert Opin Biol Ther **2006**; 6:631–633.

Keystone EC, Schiff MH, Kremer JM, Kafka S, Lovy M, DeVries T et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum **2004a**; 50:353–363.

Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human antitumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial.Arthritis Rheum **2004b**; 50:1400–1411.

Khan MA. Update on spondyloarthropathies. Ann Intern Med **2002**; 136:896–907.

Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med **1995**; 333:142–146.

Kirwan JR, Bijlsma JWJ, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev **2007**.

Klareskog L, van der Heijde D, de Jager, JP, Gough A, Kalden J, Malaise M et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet **2004**; 363:675–681.

Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum **2006**; 54:38–46.

Kraan MC, van Kuijk AWR, Dinant HJ, Goedkoop AY, Smeets TJM, de Rie MA et al. Alefacept treatment in psoriatic arthritis: Reduction of the effector T cell population in peripheral blood and synovial tissue is associated with improvement of clinical signs of arthritis. Arthritis Rheum **2002**; 46:2776–2784.

Kremer JM, Westhoven R, Leon M, Di Giorgio E, Alten R, Steinfeld S et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activationwith fusion protein CTLA-4Ig. N Engl J Med **2003**; 349:1907–1915.

Kristensen LE, Christensen R, Bliddal H, Geborek P, Danneskiold-Samsøe B, Saxne T. The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: a systematic literature review. Scand J Rheumatol **2007**; 36:411–417.

Kunz RA, Oxman AD. Empirical evidence of selection bias in studies of the effects of health care: a systematic review. Presented at the Cochrane Colloquium, Oslo, 5-8 October, **1995**.

Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum **2002**; 46:347–356.

Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum **1998**; 41:778–799.

Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med **2000**; 343:1594–1602.

MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum **2000**; 43:30–37.

Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet **1999**; 354:1932–1939.

Mander M, Simpson JM, McLellan A, Walker D, Goodacre JA, Dick WC. Studies with an enthesis index as a method of clinical assessment in ankylosing spondylitis. Ann Rheum Dis **1987**; 46:197–202.

Maugars Y, Mathis C, Vilon P, Prost A. Corticosteroid injection of the sacroiliac joint in patients with seronegative spondylarthropathy. Arthritis Rheum **1992**; 35:564–568.

McGonagle D, Conaghan PG, Emery P. Psoriatic arthritis: a unified concept twenty years on. Arthritis Rheum **1999**; 42:1080–1086.

Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet **2000**; 356:385–390.

Mease PJ, Antoni CE, Gladman DD, Taylor WJ. Psoriatic arthritis assessment tools in clinical trials. Ann Rheum Dis **2005a**; 64 (Suppl 2):49–54.

Mease PJ, Gladman D, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EHS et al. Adaliumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum **2005b**; 52:3279–3289.

Mejjad O, Daragon A, Louvel JP, Da Silva LF, Thomine E, Lauret P et al. Osteoarticular manifestations of pustulosis palmaris et plantaris and of psoriasis: two distinct entities. Ann Rheum Dis **1996**; 55:177–180.

Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum **1973**; 3:55–78.

Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med **1997**; 337:141–147.

Morrison E, Capell HA. Corticosteroids in the management of early and established rheumatoid disease. Rheumatology **2006**; 45:1058–1061.

Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet **1999**; 353:1568–1573.

Nash P, Clegg DO. Psoriatic arthritis therapy: NSAIDs and traditional DMARDs. Ann Rheum Dis **2005**; 64 (Suppl 2):74–77.

Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum **2004**; 50:1761–1769.

O'Dell JR, Leff R, Paulsen G, Haire C, Mallek J, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum **2002**; 46:1164–1170.

O'Neill T, Silman AJ. Psoriatic arthritis. Historical background and epidemiology. Baillière's Clin Rheumatol **1994**; 8:245–261.

Ortiz Z, Shea B, Garcia Dieguez M, Boers M, Tugwell P, Boonen A, et al. The responsiveness of generic quality of life instruments in rheumatic diseases. A systematic review of randomized controlled trials. J Rheumatol **1999**; 26:210–216.

Ostergaard M, Unkerskov J, Linde L, Krogh NS, Ravn T, Ringsdal VS, et al. Low remission rates but long drug survival in rheumatoid arthritis patients treated with infliximab or etanercept: results from the nationwide Danish DANBIO database. Scand J Rheumatol **2007**; 36:151–154.

Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum **2004**; 50:3085–3092.

Papanikolaou PN, Christidi GD, Ioannidis JP. Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies. CMAJ **2006**; 174:635–641.

Pincus T, Sokka T. Should Contemporary rheumatoid arthritis clinical trials be more like standard patient care and vice versa? Ann Rheum Dis **2004**; 63(Suppl 2): 32–39.

Pocock SJ, Collier TJ, Dandreo KJ, de Stavola BL, Goldman MB, Kalish LA et al. Issues in the reporting of epidemiological studies: a survey of recent practice. BMJ **2004**; 329: 883.

Prevoo ML, 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum **1995**; 38:44–48.

Ramey DR, Raynauld JP, Fries JF. The health assessment questionnaire 1992: status and review. Arthritis Care Res **1992**; 5:119–129.

Rantapää Dahlqvist SR, Jacobsson L. In: Klareskog L, Saxne T, Yvonne Enman, eds. Reumatologi. Lund: Studentlitteratur **2005;** Chapter 6.

Rennie D. CONSORT revised—improving the reporting of randomized trials [Editorial]. JAMA **2001**; 285:2006–2007.

Silman AJ, Ollier W, Holligan S, Birrell F, Adebajo A, Asuzu MC et al. Absence of rheumatoid arthritis in a rural Nigerian population. J Rheumatol **1993a**; 20:618–622.

Silman AJ, MacGregor AJ, Thomson W, Holligan S, Carthy D, Farhan A et al. Twin concordance rates for rheumatoid arthritis: results from a nationwide study. Br J Rheumatol **1993b**; 32:903–907.

Silman AJ, Newman J, MacGregor AJ. Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease-discordant twins. Arthritis Rheum **1996**; 39:732–735.

Silman AJ. Contraceptives, pregnancy, and RA. Ann Rheum Dis **2002**; 61:383.

Simonsson M, Bergman S, Jacobsson LT, Petersson IF, Svensson B. The prevalence of rheumatoid arthritis in Sweden. Scand J Rheumatol **1999**; 28:340–343.

Staren E, Essner R, Economou J. "Overview of biological response modifiers." Semin Surg Oncol **1989**; 5:379–384.

Straube RH, Harle P, Sarzi-Puttini P, Cutolo M. Tumor necrosis factor-neutralizing therapies improve altered hormone axes: An alternative mode of antiinflammatory action. Arthritis Rheum **2006**; 54:2039–2046.

Svensson B, Boonen A, Albertsson K, van der HD, Keller C, Hafström I. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. Arthritis Rheum **2005**; 52:3360–3370.

Symmons DP. Epidemiology of rheumatoid arthritis: determinants of onset, persistence and outcome. Best Pract Res Clin Rheumatol **2002**; 16:707–722.

Talpaz M, Kantarjian H, McCredie K, Trujillo J, Keating M, Gutterman J. Therapy of chronic myelogenous leukemia. Cancer **1987**; 59(Suppl): 664–667.

Taylor WJ, Harrison AA. Could the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) be a valid measure of disease activity in patients with psoriatic arthritis? Arthritis Rheum **2004**; 51:311–315.

Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, and the CASPAR study group. Classification criteria for psoriatic arthritis. Arthritis Rheum **2006**; 54:2665–2673.

The GRADE working group.Grading quality of evidence and strength of recommendations. BMJ **2004**; 328:1490–1494.

Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. J Rheumatol **2002**; 29:62–67.

Turesson C, Jarenros A, Jacobsson L. Increased incidence of cardiovascular disease in patients with rheumatoid arthritis: results from a community based study. Ann Rheum Dis **2004**; 63:952–955.

van der Heijde DM, 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis **1990**; 49:916–920.

Van Dongen H, van Aken J, Lard LR, Visser K, Ronday HK, Hulsmans HM et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controled trial. Arthritis Rheum **2007**; 56:1424–1432.

van Gestel AM, Prevoo ML, 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum **1996**; 39:34–40.

van Riel PL, van Gestel AM. Clinical outcome measures in rheumatoid arthritis. Ann Rheum Dis **2000**; 59 (Suppl 1):28–31.

van Riel PL, Schumacher HR, Jr. How does one assess early rheumatoid arthritis in daily clinical practice? Best Pract Res Clin Rheumatol **2001**; 15:67–76.

Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ et al, for the STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med **2007a**; 147:W-163–194.

Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ et al, for the STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med **2007b**; 4:297.

Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ et al, for the STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology **2007c**; 18:805–835.

Vasey FB, Espinoza LR. Psoriatic arthritis. In: Calin A, ed. Spondyloarthropathies. Orlando: Grune and Stratton, **1984**:151–85.

Verstappen SMM, Jacobs JWG, van der Veen MJ, Heurkens AHM, Schenk Y, ter Borg EJ et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis **2007**; 66:1443–1449.

Vessey MP, Villard-Mackintosh L, Yeates D. Oral contraceptives, cigarette smoking and other factors in relation to arthritis. Contraception **1987**; 35:457–464.

Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med **1999**; 340:253–259.

Weisman MH, Moreland LW, Furst DE, Weinblatt ME, Keystone EC, Paulus HE et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther **2003**; 25:1700–1721.

Wolfe F. The epidemiology of drug treatment failure in rheumatic arthritis. Baillière's Clin Rheumatol:. Int Pract Res **1995;** 9:619–32.

www.cochrane.org

www.srfonline.org

Zachariae H. Prevalence of joint disease in patients with psoriasis: implications for therapy. Am J Clin Dermatol **2003**; 4:441–447.

Zink A, Listing J D, Kary S, Ramlau P, Stoyanova-Scholz M, Babinsky K et al. Treatment continuation in patients receiving biologics or conventional DMARD therapy. Ann Rheum Dis **2005**; 64:1274–1279.

Zochling J, van der Heijde D, Burgos-Vargas R, Collantes E, Davis JC, Jr., Dijkmans B et al. ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis **2006**; 65:442–452.