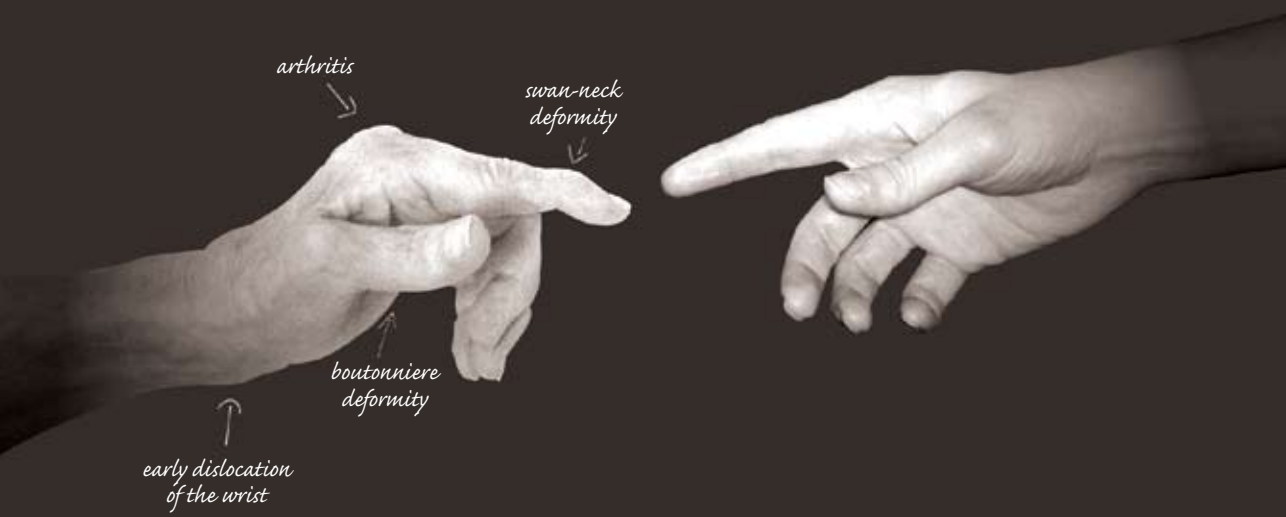
Effectiveness and safety of TNF-alpha blocking therapy in patients with rheumatoid arthritis

Marcel Flendrie



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Voor mijn ouders

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CHAPTER 1
Introduction

Summary

Over the past two decades major advances have been made in unravelling the inflammatory process in rheumatoid arthritis. A dominant role for TNFα has been implicated and has led to the development of a new class of drugs: TNFα blocking agents. Currently three TNFα blocking agents have been approved in the Netherlands for the treatment of rheumatoid arthritis: the soluble p75 TNFα receptor fusion protein Etanercept (Enbrel®), the chimerical monoclonal anti-TNFα antibody infliximab (Remicade®) and the human monoclonal anti-TNFα antibody adalimumab (Humira®).

These agents have shown remarkable efficacy and acceptable safety profiles in clinical trials. Long-term safety and effectiveness, however, need to be further elucidated in longitudinal observational studies, as important safety issues have emerged from clinical use.

At the Radboud University Nijmegen Medical Centre a longitudinal observational study was set up to monitor the long-term effectiveness and safety of TNFα blocking therapy in patients with rheumatoid arthritis (the Nijmegen Biologics Registry). The purpose of this study was to investigate clinical aspects of TNFα treatment, including, amongst others, drug survival, effectiveness, toxicity and treatment modulation, which form the major subjects of this thesis.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease, which primarily affects the joints and is characterized by inflammation of synovial joints in a symmetrical pattern. Active disease is characterised by pain, swelling and stiffness of joints in combination with raised levels of inflammatory markers. RA follows a variable disease course with remissions and exacerbations. The inflammatory process can lead to destruction of cartilage and bone, resulting in joint deformities, permanent functional impairment and disability [1]. Systemic involvement may occur and includes, amongst others, fever, fatigue, nodulosis, pulmonary fibrosis, vasculitis and serositis. Due to a large inter-individual variability in disease activity, degree of joint destruction and systemic involvement RA is a very heterogeneous disease.

The prevalence of RA has been estimated on 0.5% to 1% in populations worldwide [2]. The estimated incidence is 0.2 per 1000 in males and 0.4 per 1000 in females [3].

PATHOGENESIS OF RHEUMATOID ARTHRITIS

The exact cause of RA still remains unknown, but major advances have been made over the past two decades in understanding the inflammatory processes in RA. Experimental studies have implicated a dominant role for cytokines, like tumour necrosis factor alpha (TNFα) and interleukin-1 (IL-1) [4]. Current hypotheses assume an inappropriate immune response, triggered by a yet undiscovered exogenous or endogenous antigen. Antigen presenting cells (tissue macrophages or dendritic cells) activate CD4+ T-cells, which stimulate macrophages, monocytes and fibroblasts to produce a number of cytokines, including TNFα. This inflammatory response remains active due to a disequilibrium between proinflammatory and anti-inflammatory cytokines, and is assumably driven by dendritic cells or CD4+ T-cells [4,5]. The discovery of key proinflammatory cytokines in RA, like TNFα, has offered therapeutic targets for treatment.

TREATMENT OF RHEUMATOID ARTHRITIS

At present RA cannot be cured. Pharmacological treatment is aimed at reducing and controlling disease activity, thereby improving functional disability and preventing the destruction of joint cartilage and bone. Non-Steroidal Anti-Inflammatory drugs (NSAIDs) are used to control symptoms of pain and morning stiffness. Corticosteroids and disease modifying anti-rheumatic drugs (DMARDs), like methotrexate and leflunomide, are being used to control disease activity and to reduce the progression of cartilage and bone destruction. The observations that DMARD therapy initiated early in the course of the disease and that combining different DMARDs with each other and with corticosteroids at high doses are more effective in reducing disease activity and slowing joint destruction have led to a more aggressive pharmacological approach

of RA [6,7]. A major advance over recent years in the treatment of RA has been the introduction of biological therapies, like TNFα blocking agents.

Non-pharmacological therapies, like cooling, orthotics, physical therapy and joint surgery are aimed at controlling symptoms, like pain and stiffness, and improving functional impairment [8-11].

TNFα BLOCKING AGENTS

Alongside an improved understanding of the immune mechanisms involved in the pathogenesis of RA, a new class of drugs has been developed since the early 1990s. These so-called 'biologics' have been designed specifically at targeting and antagonizing key cytokines, thereby suppressing inflammation and preventing cartilage and bone destruction. At present drugs that inhibit TNFα are the most successful competitors of this new class of drugs in the treatment of RA. TNFα blocking agents can be divided in soluble TNFα receptors and antibodies against TNFα. Three TNFα blocking agents are currently approved for RA treatment: etanercept (soluble TNFα receptor), infliximab and adalimumab (both monoclonal anti-TNFα antibodies). The structure and activity of these agents are described below and are summarized in table 1.1.

Other TNFα blocking agents, like a pegylated p55 TNF-receptor (pegsunercept), a pegylated TNFα antibody fragment (certolizumab), humanized anti-TNFα antibodies (CDP-571, AME-527) and a fully human anti-TNF-alpha monoclonal antibody (golimumab) are currently under investigation or await approval from the regulatory agencies [12-14].

Table 1.1: characteristics of TNFα blocking agents

	Infliximab (Remicade®)	Etanercept (Enbrel®)	Adalimumab (Humira®)
Agent	Murine MoAb (IgG1)	p75-Fc IgG1 fusion protein	Human MoAb (IgG1)
Distribution volume, L (SD)	Primarily intravascular	12 (6)	4.7-6.0*
Peak plasma concentration, days (SD)		2.0-2.9 (1.4)	5.5 (2.3)
Half-life, days (SD)	7.7-9.5*	2.6-4.3 (1.3)	10-13.6*
Binding complex with	Soluble TNFα Membrane bound TNFα	Soluble TNFα Membrane bound TNFα TNFβ (lymphotoxin)	Soluble TNFα Membrane bound TNFα
Cell lysis	yes	no	yes (in vitro)

Legend: *no standard deviation given. Abbreviations: IgG = immunoglobulin G, L = litre, MoAb = monoclonal antibody, SD = standard deviation.

ETANERCEPT

Etanercept (Enbrel®) is a fusion protein of two soluble human p75 TNFα receptors, linked to the FC portion of IgG 1 [15]. It is produced in genetically engineered Chinese hamster ovary cells. Etanercept binds both soluble and cell-bound TNFα, and lymphotoxin (TNFβ) [16]. Breakdown and clearance are believed to occur through proteolysis with recycling or elimination as by-products in bile or urine. Peak plasma concentration is reached in 2 to 3 days, with a plasma half-life of approximately 3-4 days [17-20].

Etanercept is administered as subcutaneous injection and the recommended dose in RA is 25 milligram (mg) twice a week or 50 mg once a week [19,21], either as monotherapy or in combination with DMARDs.

INFLIXIMAB

Infliximab (Remicade®) is a chimeric human-mouse monoclonal anti-TNFα antibody, consisting of a murine TNFα binding region combined with a human IgG1 [22]. Infliximab binds with high affinity to cell-bound TNFα and soluble TNFα monomers and trimers and forms stable complexes [16,23]. Infliximab inhibits binding of TNFα to TNF-receptor-1 (TNF-RI or p55) and TNF-RII (p75) and it may dissociate TNFα already bound to TNF-R. Unlike etanercept, infliximab does not bind or inhibit lymphotoxin. The estimated half-life of infliximab is 7.7 to 9.5 days, although it can be detected as long as 28 weeks after infusion (mean 12 weeks) [20,24]. The half-life increases with higher doses and decreases with anti-infliximab antibody formation, which occurs in 8-17% of RA patients [24-27].

Current treatment recommendations in RA state a starting dose of 3 mg/kg body weight, administered intravenously at 0, 2 and 6 weeks, followed by eight-weekly infusions thereafter. In case of insufficient response it is possible to increase the dose or to reduce the interval to 4 weeks [24]. Although in clinical practice a maximum corresponding dose of 10 mg/kg per 8 weeks has been used in patients with insufficient response, the European Commission has recently approved a maximum dose of 7.5 mg/kg per 8 weeks, which has been adapted by the regulatory authorities in the Netherlands as the maximum dose [28].

ADALIMUMAB

Adalimumab (Humira®) is a fully human monoclonal antibody directed against TNFα. It is derived by phage-display techniques. Adalimumab binds both soluble TNFα and cell-bound TNFα and can lyse TNFα-expressing cells in the presence of complement [20,29]. In theory, adalimumab is less immunogenic than other TNFα blocking agents. The estimated half-life of adalimumab is 10-14 days, which slightly increases with higher age and higher dose [20,30-32].

Adalimumab is administered subcutaneously at a recommended starting dose of 40 mg every two weeks with the possibility of reducing the interval to one week in case of insufficient response [30]. It has been approved as monotherapy or in combination with DMARDs.

EFFICACY OF TNFα BLOCKING AGENTS

Efficacy of etanercept was shown in randomized clinical trials (RCTs) in patients with established RA, both as monotherapy [33-35] and in combination with DMARDs [36,37]. In patients with early RA treatment with etanercept resulted in a more rapid improvement and less adverse events than methotrexate (MTX) [38]. The combination of etanercept and MTX has been shown to reach higher efficacy than either etanercept or MTX alone [36,37]. Reported effects were sustained in open-label extension trials with 3 to 4 years follow-up both for monotherapy and for combination therapy with MTX [39-42].

Efficacy of infliximab has been shown in RCTs as monotherapy [43,44] and in combination with methotrexate in patients with established RA [26,45] and patients with early RA [46,47]. Reported efficacy was sustained over a two-year period [48]. Combination therapy with methotrexate resulted in higher response rates, compared to infliximab monotherapy [26]. The combination provided evidence for a possible synergism by reducing the development of anti-infliximab antibodies and increasing serum infliximab levels [26].

Adalimumab efficacy has been shown in RCTs with long-term RA patients for monotherapy and for combination therapy with MTX [32,49-51]. Sustained efficacy was shown in combination with methotrexate over a four-year follow-up period [52]. Combining adalimumab with methotrexate showed higher response rates than adalimumab monotherapy in patients with early, active RA [53].

SAFETY OF TNFα BLOCKING AGENTS

Safety profiles from RCTs with RA patients are generally considered acceptable for all three agents [36,38,41,45,47,50]. The most common reported adverse events associated with TNFα blocking therapy include infusion and injection reactions. Other adverse events associated with TNFα blocking therapy in RCTs are infections, like the reactivation of latent tuberculosis, and skin disease, like vasculitis. Most control arms in RCTs added placebo to background methotrexate. The limited number of studies with true placebo control arms also reported no differences, except for one study which reported statistically significantly more incidences of headache and skin rash in patients on adalimumab [49].

From post-marketing observations more adverse events have been attributed to TNFα blocking therapy, including drug-induced SLE, demyelinating disease and worsening of heart failure. Further concern exists regarding the occurrence of malignancies, especially lymphoma's [54].

Following the important role of TNFα in immune responses, inhibition of TNFα has raised concerns regarding the occurrence of serious adverse events, especially serious infections and malignancies. Although most RCTs did not suggest an increases risk for serious infections, some trials reported an increased risk for serious infections in patient groups treated with adalimumab or infliximab in combination with methotrexate, both compared to patients on placebo plus methotrexate [47,50,53,55]. Also, the rate of serious infections was higher in patients on adalimumab plus methotrexate, compared to adalimumab monotherapy (2.3 versus 0.7 events per 100 patient years (pt-yr)) [53]. A recent meta-analysis, combining data of adalimumab and infliximab RCTs, reported an increased risk for serious infections [56], including pneumonia, a reactivation of latent tuberculosis , urinary tract, skin and soft tissue infections, infection with *Herpes zoster* and *Histoplasma* [26,27,47,50,51,53,55].

Observational studies have also reported the reactivation of tuberculosis, as well as infections with intracellular pathogens and opportunistic infections [57-60]. The first line of defence against Mycobacterium tuberculosis is the formation of granulomas by macrophages, stimulated by TNFα. This mechanism is impaired by TNFα blockade and accounts for the numerous reports of reactivation of tuberculosis, as well as the relative frequent disseminated state of the infection [61-63]. The susceptibility for reactivation of latent tuberculosis and other granulomatous infections might be higher in monoclonal antibodies like infliximab, compared to soluble receptor fusion proteins, like etanercept. This difference possibly results from the induction of leukocyte apoptosis by monoclonal antibodies [61,62].

Another major concern is the development of malignancies, especially lymphoma's, following TNFα blocking therapy. At present, there is no clear answer but it is believed possible that TNFα blocking therapy might add to an already increased background risk for lymphoma's in RA patients, resulting from altered immune responses by the disease itself and by the use of immunosuppressive drugs [64]. A meta-analysis including nine placebo-controlled trials with infliximab and adalimumab showed a significant increased risk for malignancies in high-dose treatment arms [56]. Ten out of 24 encountered non-skin malignancies were lymphomas.

Other important adverse events associated with the use of TNFα blocking agents include demyelinating disease, drug-induced lupus and worsening of pre-existent heart failure [58,65-67]. Current prescription guidelines state NYHA class III/IV to be an absolute contra-indication for therapy with [24]. Relative contra-indications for all TNFα blocking agents are chronic infection, including latent tuberculosis and hepatitis B virus carrier state, demyelinating disease, malignancy, hepatic failure, pregnancy and breast-feeding [24,30,54,68].

MONITORING EFFECTIVENESS AND SAFETY OF TNFα BLOCKING AGENTS

Several large post-marking studies have been initialised, mainly in Europe and in the United States. The rationale for these so-called biologic registries was to facilitate detailed data collection on long-term safety and effectiveness [69]. Examples of these

registries are the BSR Biologics Registry in England, the Swedish registries STURE and STAGG, and the German RABBIT registry [70-72].

Registries use pre-specified monitoring protocols for follow-up, which can include standardized measures of disease activity, radiographic evidence of progression and functional capacity. A well validated and widely used measurement of disease activity is the Disease Activity Score (DAS28), a composite index consisting of the erythrocyte sedimentation index, 28-joint counts for swelling and tenderness and a patient assessed general health score on a visual analogue scale [73,74].

Monitoring and analysis of long-term safety are aided by standardized adverse event recording systems, which facilitate coding and grading of adverse events. Examples are the Rheumatology Common Toxicity Index or the MedDRA system [75,76].

THE NIJMEGEN BIOLOGICS REGISTRY

The Nijmegen Biologics Registry was set up as a longitudinal observational study for monitoring TNFα blocking therapy in RA patients [77]. The registry investigates several clinical aspects of TNFα blocking therapy, including, amongst others, drug survival, effectiveness, toxicity and treatment modulation, which form the subject of this thesis.

In this registry all patients were monitored who started on biologic therapy at the rheumatology departments of the Radboud University Nijmegen Medical Centre (RUNMC) and the St Maartenskliniek Nijmegen (SMN), a categorical hospital. Patients' characteristics were collected at start and information on TNFα blocking therapy, second-line therapy, disease activity (DAS28) and adverse events (AEs) were collected 3-monthly during therapy and 1-yearly after stop, according to a standardized protocol. Data were entered into an electronic patient registry, developed in collaboration with the department of Medical Technology Assessment for long term registration and monitoring of RA patients.

OUTLINE OF THE THESIS

The objective of this thesis was to study the drug survival, effectiveness and safety of TNFα blocking therapy in RA patients, as well as treatment modulations of infliximab therapy. The content of the chapters in this thesis is outlined below.

Chapter two investigates long-term drug-survival, effectiveness and safety of etanercept, infliximab and adalimumab in RA patients in the Nijmegen Biologics Registry. Drug survival was investigated overall and for different reasons of drug discontinuation. Effectiveness was investigated using the disease activity score (DAS28) and the European League Against Rheumatism (EULAR) criteria for response and remission [73,78]. All adverse events were grouped according to an adverse events index, adapted from the Proposed Rheumatology Common Toxicity Index [79].

The chapter also describes the predictive value of patient, disease and concomitant therapy characteristics at baseline for drug-survival, effectiveness and adverse events, investigated in multivariate analysis.

In **chapter three** the effectiveness and safety of the combination of infliximab and leflunomide is studied. Combining two or more DMARDs can enhance efficacy by additive or synergistic effects [80]. In RCTs the only drug combined with infliximab has been methotrexate. Leflunomide may be an important alternative for combination therapy in patients who do not respond to or do not tolerate methotrexate. This chapter described the disease activity, treatment response and safety of infliximab administration after or simultaneously with leflunomide in RA patients, in comparison to patients not using leflunomide. Due to the long half-life of leflunomide two separate analyses were carried out. The first included all patients who had used leflunomide during infliximab therapy or within six months prior to starting infliximab. The second analysis was performed with the leflunomide group consisting only of patients on active leflunomide. Furthermore, in a subanalysis the incidence of antinuclear antibodies (ANA) at start and seroconversion to ANA positivity during TNFα blocking therapy was studied, together with the predictive value of ANA positivity on effectiveness and safety.

Chapter four describes an open-label study in which the course of the disease activity and the response to therapy was evaluated in RA patients starting on infliximab therapy. The disease activity in patients with a moderate response after 14 weeks was closely observed during the next 8 week interval and the pattern was used to guide adjustments of infliximab therapy. This strategy was based on the hypothesis that part of the moderate responders might in fact have a good but short-lived response and thus flare before the next infliximab infusion has been administered. This hypothesis is based on previous observations showing a large variation in both dosage and time interval needed to maintain low disease activity [81,82], which might result from individual variations in pharmacokinetics of infliximab [83].

Next to the frequent reports of skin reactions in RCTs, various dermatological conditions have been reported after the use of TNFα blocking agents in RCTs and clinical practice. Some conditions were severe and lead to hospital admission or withdrawal of TNFα blocking therapy. In **chapter five** a prospective study is described investigating clinically important dermatological conditions in RA patients receiving TNFα blocking therapy. The number and nature of the dermatological conditions are described in detail, including time-relations, comedication, histological findings and treatment. Patient on TNFα blocking agents experiencing a dermatological reaction, resulting in a dermatological consultation, were compared with a control group, naive to TNFα blocking therapy and matched for follow-up period.

Psoriasiform skin reactions occurring during TNFα blocking therapy are paradoxal and interesting phenomena, as etanercept, infliximab and adalimumab have recently been registered for plaque psoriasis after promising results in RCTs [19,24,84].

Chapter six describes in detail the de novo development of psoriasiform skin lesions in five RA patients and reviews the literature concerning 110 cases of patients developing psoriasiform lesions during TNFα blocking therapy.

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CHAPTER 2

Treatment with infliximab, adalimumab and etanercept; drug survival, effectiveness, safety and their predictors in patients with rheumatoid arthritis

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Summary

Objective | To investigate drug survival, effectiveness and safety of TNFα blocking agents and their predictors in RA patients.

Methods | All RA patients, starting with infliximab, etanercept or adalimumab at two hospitals were followed prospectively. Patients' characteristics were collected at start and information on TNFα blocking therapy, second-line therapy, disease activity (DAS28) and adverse events (AEs) were collected 3-monthly during therapy and 1-yearly after stop. Predictive factors for drug survival, DAS28 over time and AEs were analyzed by multiple regression analyses.

Results | 492 patients were included: 368 infliximab, 94 adalimumab, 30 etanercept. Baseline characteristics indicated longstanding severe RA. Overall drug-survival rates after year 1, 2 and 3: 63%, 42% and 34%. Longer drug survival was predicted by concomitant MTX or non-MTX DMARD therapy, compared to monotherapy.
Overall responses over time were: moderate 41-49%, good 22-33%, remission 12-24%. DAS28 over time was predicted by monotherapy, gender, age, baseline DAS28, DMARD history and corticosteroid use.
1199 AEs were recorded (105/100pt-yrs), mostly infections (38%) and dermatological conditions (15%). Major AEs during therapy: infliximab 15/100pt-yrs, adalimumab 17/100pt-yrs, etanercept 7/100pt-yrs. Infections were predicted by concomitant MTX therapy and steroid use. Other adverse events were predicted by weight, age, gender and DMARD history.

Conclusion | This prospective study in patients with longstanding severe RA showed lower drug-survival rates of TNFα blocking therapy, compared to previous reports. Disease activity over time did not differ between TNFα blocking agents. Both drug-survival and effectiveness of TNFα blocking agents was positively influenced by the use of concomitant DMARDs, including MTX. Concomitant MTX and corticosteroids were independently associated with an increased risk for infections.

INTRODUCTION

Tumour necrosis factor alpha (TNFα) plays an important role in the pathogenesis of rheumatoid arthritis (RA) [1]. Currently two monoclonal anti-TNFα antibodies (infliximab and adalimumab) and one soluble TNFα receptor (etanercept) are being used in RA clinical practice, after demonstration of remarkable efficacy and acceptable safety profiles in clinical trials [2-4].

However, clinical trials are not designed to provide information on long-term safety and efficacy and on the occurrence of rare adverse events. Furthermore, trial designs often exclude patients with serious comorbidity and carry restrictions on the use of comedication. These factors influence extrapolation of efficacy and safety results from trials to the RA population in daily clinical practice [5]. Furthermore, several safety issues have arisen after clinical use, including, amongst others, reactivation of tuberculosis, opportunistic infections, demyelinating disease and drug-induced lupus [6-8].

These arguments stress the importance of post-marketing observational studies investigating effectiveness and safety of long-term use of TNFα blocking therapy. All patients on TNFα blocking therapy at the Radboud University Nijmegen Medical Centre and the Sint Maartenskliniek Nijmegen are being followed in longitudinal observational study, focusing on long-term effectiveness and safety of TNFα blocking agents [9]. The aim of the study presented here was to describe the long term survival, effectiveness and safety of TNFα blocking therapy and to investigate the predictive value of baseline and treatment characteristics, including concomitant DMARDs and corticosteroids, for drug-survival, long-term effectiveness and safety of TNFα blocking agents in RA patients.

PATIENTS AND METHODS

All consecutive RA patients, fulfilling the 1987 American College of Rheumatology (ACR) criteria [10], who started TNFα blocking therapy, were followed as part of a Biological Registry in the Netherlands [9]. Patients were required to meet the Dutch guidelines for biological therapies: moderate to high disease activity (DAS28 ≥ 3.2) and failure or intolerability of at least two disease modifying antirheumatic drugs (DMARDs), including methotrexate in adequate dosages.

Patients were recruited at Rheumatology departments of two participating centres: the Radboud University Nijmegen Medical Centre (RUNMC) and the St Maartenskliniek Nijmegen (SMN), a categorical hospital. All RA patients who had started TNFα blocking therapy before January the 1st 2004 were included in this prospective study.

Therapy

Infliximab (INF) and etanercept (ETA) therapy were administered in daily clinical practice. Adalimumab (ADA) was administered in clinical trials.

Daily clinical practice: Therapy was started according to recommendations by the manufacturer, i.e. INF intravenously (i.v.) 3 milligram per kilogram (mg/kg) body

weight at weeks 0, 2 and 6 and 8-weekly thereafter, and ETA subcutaneously (s.c.) 25 mg twice weekly. Dose or interval changes were made according to the judgement of the treating rheumatologist. INF doses were rounded up to 10 mg (SMN) or to 100 mg (RUNMC).

Clinical trials: ADA was administered intravenously or subcutaneously. After completion of phase 1 and 2 trials all patients entered an open-label extension phase and received 40 mg subcutaneously every other week with the possibility of a dose increase to 40 mg every week in case of insufficient response, similar to daily clinical practice.

Measurements

Patients entered a standardized monitoring protocol at start of TNFα blocking therapy consisting of three monthly visits during therapy and one-yearly visits after discontinuation of TNFα blocking therapy. At baseline age, gender, weight, disease duration, rheumatoid factor (RF), anti-nuclear antibodies (ANA), the number of previously used DMARDs, current DMARD therapy, oral or intramuscular corticosteroid use were collected. At each visit erythrocyte sedimentation rate (ESR), 28 joint counts for swelling and tenderness and a visual analogue scale for general well-being were collected for calculation of the disease activity score (DAS28) [11], as well as dose and interval changes of TNFα blocking agents, concomitant DMARD and corticosteroid therapy. Date and reason for discontinuation were recorded in case of treatment discontinuation.

Adverse events (AE) and exacerbations of pre-existing diseases were recorded, if considered clinically important by the treating physician, and classified according to an adverse events index, adapted from the Proposed Rheumatology Common Toxicity Index [12]. They were graded into minor or major events; the latter defined as any event requiring hospitalization or being considered potentially life threatening.

STATISTICAL ANALYSIS

TNFα blocking therapy

Analyses for drug-survival, effectiveness and adverse events were performed with RA patients, who were naïve to TNFα blocking therapy. Patients were grouped according to the first TNFα blocking they used. Baseline characteristics were compared between the groups using chi-square test or one-way analysis of variance (ANOVA). Variables were transformed to obtain normality, if appropriate. Total follow-up time, time on TNFα blocking therapy and time after discontinuation of therapy (time off therapy) was calculated for each patient (patient-years (pt-yrs) of follow-up).

Drug survival and reasons for discontinuation

The number and percentages of patients permanently discontinuing TNFα blocking agents were calculated for different reasons of discontinuation.

Drug-survival to permanent discontinuation of the first course of TNFα blocking therapy was investigated for the TNFα blocking agent overall and separately for

discontinuation due to ineffectiveness and adverse events (Kaplan-Meyer, censoring date January 1st 2004).

The predictive value of baseline characteristics (age, gender, weight, disease duration, baseline DAS28, RF positivity, ANA positivity, number of previously used DMARDs, the use of concomitant DMARD therapy and the use of prednisone at baseline) on drug survival was investigated using Cox regression analysis. Concomitant DMARD therapy was grouped in patients using methotrexate (MTX group), patients using other DMARDs (non-MTX group) and patients on monotherapy with TNF-blocking agents. Hazard ratio (HR) and p-values were calculated. A staged approach to model building was used and models were corrected for treatment centre and TNF-blocking agent. Variables with p-values greater or equal to 0.10 were excluded from the models.

Switching of TNFα blocking agents

Drug-survival of second treatment courses were explored overall and for each TNFα blocking agent separately.

Effectiveness

The DAS28 over time was investigated in two models: intention to threat (ITT) and last observation carried forward (LOCF) in which the last DAS28 value when the patient used TNFα blocking treatment was carried forward. Percentages of response and remission, according to the EULAR-criteria [13,14] were calculated after 6, 12, 24 and 36 months of treatment overall and for each TNFα blocking agent separately (ITT).

The influence of baseline characteristics on the DAS28 over time was investigated by GEE with correction for treatment centre and TNFα blocking agent. For the GEE the exchangeable correlation structure was found to be appropriate and the identity link function and the Gaussian variance model were applied.

Since the patients in this study were not randomized and the patients using ADA started treatment in an RCT setting drug survival and effectiveness are not formally statistically tested and the estimated values should be interpreted with caution.

Adverse events

The number of adverse events per pt-yr of follow-up was calculated for the total follow-up period and during active therapy, including a period up to one month after discontinuation to account for carry-over effects.

The predictive value of baseline characteristics on the occurrence of adverse events during the first course of TNFα blocking agent was tested using multivariate logistic regression analysis with correction for first TNFα blocking agent, treatment centre and duration of treatment with first TNFα blocking agent. Independent variables were considered the occurrence of any adverse event, infection, allergic reaction, dermatological event, and major events (all dichotomized).

Analyses were performed using SAS statistical software (version 8.0, SAS Institute Inc, USA), and SPSS statistical software (version 12.0, SPSS Inc, USA). P-values less than 0.05 were considered as statistically significant.

RESULTS

TNFα blocking therapy was initiated in 492 RA patients, who were naïve to TNFα blocking therapy: INF in 368 (75%) patients (RUNMC 146, SMN 222), ADA in 94 (19%) patients (all RUNMC) and ETA in 30 (6%) patients (RUNMC 18, SMN 12).

Baseline characteristics of the groups are presented in table 2.1, showing statistically significant differences in RF positivity, ANA positivity, DMARD history and concomitant DMARDs or corticosteroids use.

Table 2.1. Patient characteristics

	Infliximab n=368	Adalimumab n=94	Etanercept n=30	Total group N=492	p-value
Age, mean (SD)	56.4 (12.7)	55.6 (11.9)	52.0 (14.4)	56.0 (12.7)	n.s.
Male gender, %	94 (25.5)	34 (36.1)	8 (26.8)	136 (27.6)	n.s.
RA duration, mean (SD)	11.2 (8.9)	11.2 (8.4)	12.3 (13.3)	11.2 (9.1)	n.s.
RF positive, %	299 (81.3)	89 (94.7)	26 (86.7)	414 (84.1)	0.007
DAS28, mean (SD)	5.8 (1.1)	6.1 (1.0)	6.1 (1.5)	5.9 (1.1)	n.s.
ANA positive, %	165 (44.8)	26 (27.7)	8 (26.8)	199 (40.4)	0.004
Previous DMARD use, mean (SD)	3.9 (1.7)	4.4 (1.9)	4.2 (2.0)	4.0 (1.8)	0.03
Concomitant corticosteroids and DMARDs					
Patients on corticosteroids, %	101 (27.4)	48 (51.1)	12 (40.0)	161 (32.7)	0.001
Prednisolone dose, median (range)	7.5 (2.5-30)	10 (2.5-15)	5.0 (4-15)	10 (2.5-30)	n.s.*
Patients on concomitant DMARDs, %	288 (78.3)	16 (17.0)	17 (56.7)	321 (65.2)	0.001
• One DMARD	248 (67.4)	16 (17.0)	13 (43.3)	277 (56.3)	
- MTX	150 (40.8)	16 (17.0)	6 (20.0))	172 (35.0)	
- Other**	98 (26.6)	-	7 (23.3)	105 (21.3)	
• Two DMARDs	37 (10.1)	-	4 (13.3)	41 (8.3)	
- Including MTX	32 (8.7)	-	4 (13.3)	36 (7.3)	
- Other	5 (1.4)	-	-	5 (1.0)	
• Three DMARDs	3 (0.8)	-	-	3 (0.6)	

*after Log transformation. **in descending frequency: azathioprine 11%, leflunomide 6%, sulphasalazine 3%, hydroxychloroquine 1%, cyclosporine and parenteral gold <1%.

TNFα blocking therapy

Total follow-up time was 1147 pt-yrs: 452 pt-yrs INF, 296 pt-yrs ADA, 130 pt-yrs ETA and 269 pt-yrs off therapy. Maximum follow-up time for INF, ADA and ETA were 45, 79 and 42 months, respectively. During follow-up 53 patients were lost-to-follow-up (30 residential move, 22 deceased, 1 unknown).

Treatment adjustments of first treatment courses with TNFα blocking agents: 290 treatment changes were applied for INF in 165 patients (45%; 122 dose increases, 142 interval reductions, 11 dose-reductions and 15 interval increases). Interval reductions of ADA ('open-label' phase only) were applied in 33 patients (35%). Two interval reductions and one interval increase were applied in 3 ETA treated patients (10%).

Drug survival and reasons for discontinuation

Overall drug survival rates of 1st treatment course after the 1st, the 2nd and the 3rd year of therapy were 63%, 42% and 34%. Figure 2.1A shows the drug survival for all patients and figures 2.1B, C and D show drug survival for the three TNFα blocking agents separately. The mean survival time for INF, ADA and ETA was 20.4, 47.8 and 21.0 months, respectively. Statistical comparison between the three agents was not considered appropriate (see before).

A longer drug survival was predicted by concomitant MTX therapy (HR (95% CI) 0.50 (0.37-0.61), $p<0.001$) or by non-MTX DMARD therapy (HR (95% CI) 0.59 (0.42-0.83), $p<0.005$), compared to monotherapy. A longer survival to ineffectiveness was predicted by concomitant MTX therapy (HR 0.48 (0.27-0.82, $p<0.0001$), but not by non-MTX DMARDs (HR 0.82 (0.46-1.48), $p=0.5$). A longer survival to discontinuation because of adverse events was associated with both concomitant MTX therapy (HR 0.53 (0.36-0.80), $p<0.0001$) and non-MTX DMARDs (HR 0.50 (0.30-0.83), $p<0.01$), as well as a shorter disease duration (HR 1.02 (1.002-1.04), $p<0.05$).

Age, gender, weight, baseline DAS28, RF positivity, ANA positivity, the number of previously used DMARDs and the use of prednisone at baseline did not predict drug survival in multivariate analysis.

Overall, TNFα blocking therapy was temporarily discontinued 188 times in 115 patients (24%) and permanently discontinued in 272 patients (55%). Reasons for discontinuation are presented in table 2.2.

Switching of TNFα blocking agents

168 Patients (34%) switched to other TNFα blocking agents (See table 2.2). Overall drug survival of 2nd treatment courses was comparable with 1st treatment courses. The largest group consisted of patients switching from INF to ETA (n=121 (25%): AE 70, ineffectiveness 28, other reasons 23). Exploring drug survival of ETA as second TNFα blocking therapy after INF showed a comparable drug survival for different reasons of INF discontinuation (Log rank p=0.73).

Figure 2.1. Drug survival of TNFα blocking agents

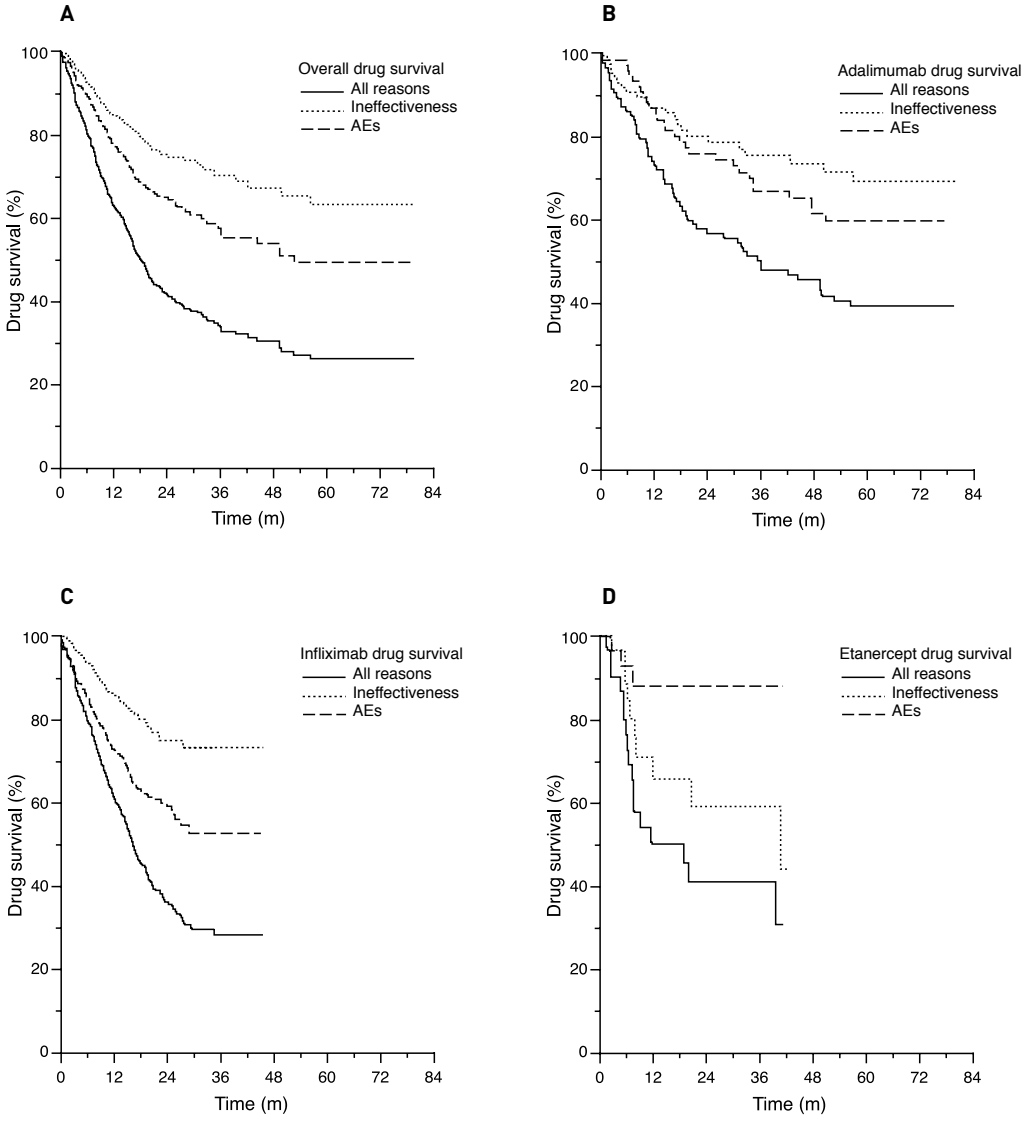


Figure 2.1A shows the drug survival of the three agents combined. Figures 2.1B, 2.1C and 2.1D show the drug survival of adalimumab, infliximab and etanercept, respectively. Solid line is overall drug survival, dotted line is survival to ineffectiveness, dashed line is survival to AE.

Table 2.2. Reasons for discontinuation

	Infliximab (n=368) n (%)*	Adalimumab (n=94) n (%)	Etanercept (n=30) n (%)	Total group (N=492) n (%)
Temporary discontinuation**	78/71 (19.3)	105/40 (42.6)	5/4 (13.3)	188/115 (23.4)
Adverse events	70/64 (17.4)	44/30 (31.9)	0/0	114/94 (19.1)
Surgery	3/3 (0.8)	44/26 (27.7)	2/2 (6.7)	49/31 (6.3)
Other reasons	5/5 (1.4)	17/13 (13.8)	3/2 (6.7)	25/20 (4.1)
Permanent discontinuation	199 (54.1)	54 (57.4)	16 (53.3)	269 (54.6)
Ineffectiveness	58 (15.8)	23 (24.5)	10 (33.3)	91 (18.5)
Adverse events	112 (30.4)	28 (29.8)	3 (10)	143 (29.1)
Other reasons	29 (7.9)#	3 (3.2)	3 (10)	35 (7.1)
Switch to other TNFα blocking agents	132 (35.9)	24 (25.5)	12 (40.0)	168 (34.1)
Switch to DMARDs	67 (18.2)	30 (58.5)	4 (13.3)	101 (20.5)
Continuing	169 (45.9)	40 (42.6)	14 (46.7)	223 (45.3)

Reasons for discontinuation of TNFα blocking agent first treatment courses. *No. of patients (% of patients), unless stated otherwise. **Displayed are no. of events/no. of patients (% of patients).
22 of 29 patients stopped infliximab because of availability of etanercept.

Effectiveness

Baseline DAS28 values were available for 486 patients (99%) and follow-up DAS28 for 3959 of 4858 visits (81%). Table 2.3 shows EULAR-response and remission percentages. Overall responses varied between 41% and 49% for moderate response, between 22% and 33% for good response and between 12% and 24% for remission.

Figure 2 shows the mean DAS28 per TNFα blocking agent over the first thee years. For ADA the mean DAS28 (95% CI) at year 4, 5 and 6 were respectively 4.0 (3.6-4.4), 4.3 (3.9-4.6) and 4.0 (3.3-4.6).

Factors independently associated with a higher disease activity over time were: Female gender, younger age, higher baseline DAS28, higher number of previously used DMARDs, the use of concomitant corticosteroids and the absence of concomitant DMARD therapy at baseline (table 2.4).

Table 2.3. Patients fulfilling EULAR response and remission criteria and mean DAS28*

	3 months n (%)**	6 months n (%)	1 year n (%)	2 years n (%)	3 years n (%)
Infliximab (n=368)	312	253	214	121	38
No response	87 (27.9)	86 (34.0)	71 (33.2)	24 (19.8)	7 (18.4)
Moderate response	147 (47.1)	105 (41.5)	88 (41.1)	53 (43.8)	18 (47.4)
Good response	78 (25.0)	62 (24.5)	55 (25.7)	44 (36.4)	13 (34.2)
Remission	*47 (15.1)*	*35 (13.8)*	*30 (14.0)*	*28 (23.1)*	*10 (26.3)*
DAS28, mean (SD)	4.17 (1.48)	4.21 (1.47)	4.19 (1.43)	3.77 (1.29)	3.70 (1.37)
Adalimumab (n=94)	86	86	79	61	56
No response	28 (32.6)	27 (31.4)	23 (29.1)	13 (21.3)	10 (17.9)
Moderate response	47 (54.7)	36 (41.9)	40 (50.6)	32 (52.5)	27 (48.2)
Good response	11 (12.8)	23 (26.7)	16 (20.3)	16 (26.2)	19 (33.9)
Remission	*6 (7.0)*	*14 (16.3)*	*7 (8.9)*	*11 (18.0)*	*12 (21.4)*
DAS28, mean (SD)	4.65 (1.38)	4.31 (1.54)	4.39 (1.52)	3.98 (1.42)	3.86 (1.38)
Etanercept (n=30)	13	17	15	11	10
No response	4 (30.8)	8 (47.1)	6 (40.0)	5 (45.5)	3 (30.0)
Moderate response	7 (53.8)	5 (29.4)	6 (40.0)	5 (45.5)	5 (50.0)
Good response	2 (15.4)	4 (23.5)	3 (20.0)	1 (9.1)	2 (20.0)
Remission	*1 (7.7)*	*3 (17.6)*	*1 (6.7)*	*1 (9.1)*	*2 (20.0)*
DAS28, mean (SD)	4.39 (1.33)	4.35 (1.88)	4.30 (1.33)	4.84 (1.51)	4.33 (1.83)
Total group (n=492)	411	356	308	193	104
No response	119 (29.0)	121 (34.0)	100 (32.5)	42 (21.8)	20 (19.2)
Moderate response	201 (48.9)	146 (41.0)	134 (43.5)	90 (46.6)	50 (48.1)
Good response	91 (22.1)	89 (25.0)	74 (24.0)	61 (31.6)	34 (32.7)
Remission	*54 (13.1)*	*52 (14.6)*	*38 (12.3)*	*40 (20.7)*	*24 (23.1)*
DAS28, mean (SD)	4.28 (1.52)	4.24 (1.47)	4.25 (1.49)	3.88 (1.45)	3.85 (1.46)

*intention to treat analysis. ** unless stated otherwise

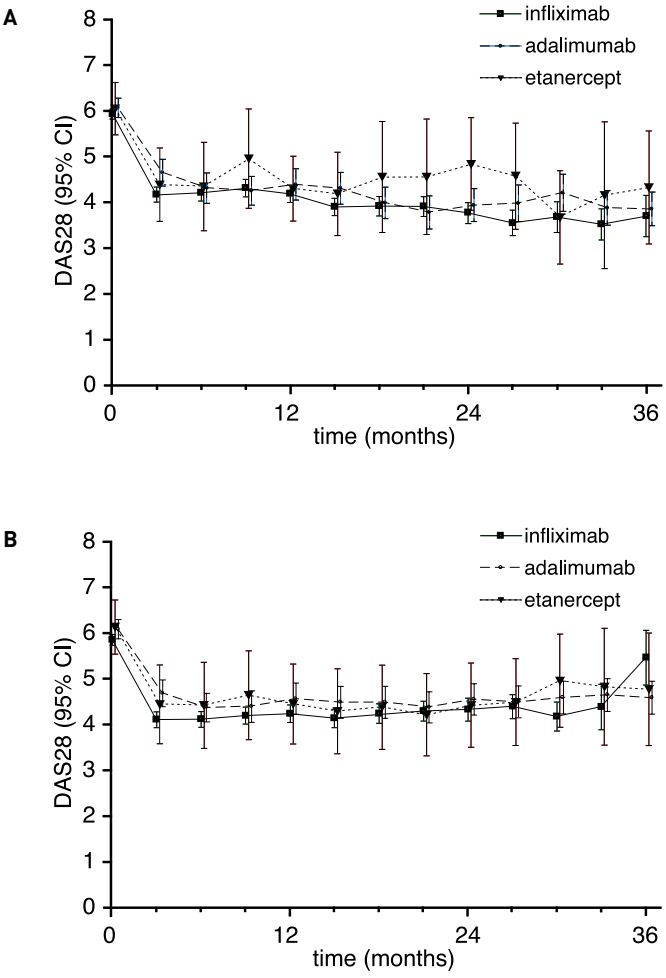
Table 2.4. Model for predictive factors for high disease activity over time

Baseline variables	Estimate	SE**	95% CI#	p-value
Age*	0.014	0.004	0.007-0.02	0.0002
Female gender	0.48	0.10	0.29-0.67	<0.001
Number of prior DMARDs	0.08	0.03	0.03-0.13	0.003
DAS28	0.45	0.04	0.38-0.52	<0.0001
Concomitant DMARDs	-0.35	0.11	-0.15- -0.56	0.0008
Prednisolone	0.20	0.09	0.02-0.39	0.03

Analysis of GEE parameter estimates. *Age: estimate per one year increment.

**Standard error, #95% confidence interval

Figure 2.2. Disease activity over the first three years



Disease activity (DAS28) over the first three years for infliximab (solid line), adalimumab (dashed line) and etanercept (dotted line). Error bars indicate 95% confidence intervals. Figure 2.2A: ITT analysis. Figure 2.2B: LOCF analysis.

Table 2.5. Allergic reactions and major adverse events during TNFα blocking therapy

	Total		Infliximab		Adalimumab		Etanercept	
	n	rate*	n	rate*	n	rate*	n	rate*
Allergic reactions								
Infusion reactions	111	12,5	106	23,1	5	5,6[#]	-	-
Acute reactions**	93	10,4	88	19,2	5	5,6	-	-
Delayed systemic reactions	18	2,0	18	3,9	0	0,0	-	-
Injection reactions	26	2,9	1	0,2	14	6,7[$]	11	8,3
Local reactions	20	2,2	1	0,2	12	5,7	7	5,3
Systemic reactions	6	0,7	0	0,0	2	1,0	4	3,0
Exanthema/erythema	52	5,8	33	7,2	12	5,7	7	5,3
Major AEs								
Infections	41	4,6	24	5,2	14	4,7	3	2,3
Pneumonia	12	1,3	9	2,0	3	1,0	0	0,0
Sepsis	4	0,4	1	0,2	3	1,0	0	0,0
Septic arthritis	7	0,8	2	0,4	4	1,3	1	0,8
Bacterial skin infections	7	0,8	4	0,9	2	0,7	1	0,8
Other major infections	11	1,2	8	1,7	2	0,7	1	0,8
Malignancy	10	1,1	4	0,9	5	1,7	1	0,8
Non-skin	8	0,9	3	0,7	4	1,3	1	0,8
Skin	2	0,2	1	0,2	1	0,3	0	0,0
Other major AEs								
Myocardial infarction	15	1,7	8	1,7	7	2,3	0	0,0
Cardiovascular other	7	0,8	4	0,9	3	1,0	0	0,0
Neurological	20	2,2	10	2,2	8	2,7	2	1,5
Allergic	9	1,0	6	1,3	2	0,7	1	0,8
Pulmonary	5	0,6	3	0,7	2	0,7	0	0,0
Gastrointestinal	4	0,4	1	0,2	1	0,3	2	1,5
Renal disease	4	0,4	1	0,2	3	1,0	0	0,0
Dermatological	3	0,3	1	0,2	2	0,7	0	0,0
Rheumatological	3	0,3	3	0,7	0	0,0	0	0,0
Other major AEs	8	0,9	3	0,7	5	1,7	0	0,0
Total major AEs	129	14,5	68	14,8	52	17,3	9	6,8

*Rate in number of events per 100 pt-yrs. **acute systemic and/or dermatological reactions.
[#]adalimumab intravenously. [$]adalimumab subcutaneously.

Adverse events

A total of 1199 adverse events (AEs) were recorded in 376 (76%) patients, naïve to TNFα blocking therapy (event rate 104.6 events per 100 pt-yrs):

- 1126 AEs (94%) occurred during active therapy (126.4 AE/100pt-yrs).
- 160 AEs (13%) led to permanent discontinuation of TNFα blocking therapy in 137 (28%) patients (18.0 AE/100pt-yrs).

The most frequently reported AEs included infections (457 AEs (38%) in 223 patients (45%)), dermatological conditions (183 AEs (15%) in 133 patients (27%)) and allergic reactions (141 AEs (12%) in 109 patients (22%)).

Major AEs were reported 155 times (13%) in 109 (22%) patients. Major AEs occurring during therapy (n=129, 11%) are shown in table 2.5. Baseline factors, predictive for the occurrence of adverse events are shown in table 2.6. Concomitant steroid use was associated with the occurrence of any AE, with infections and with the occurrence of major AEs. Concomitant use of MTX, but not non-MTX DMARDs, was associated with the occurrence of infections.

Table 2.6. Predictive variables for adverse events in multivariate logistic regression models*

Independent variable**	Predictive variables	Odds ratio (95% CI)	P-value
Any adverse event	Concomitant steroid use	2.10 (1.26-3.49)	<0.005
	Weight##	1.25 (1.05-1.48)	<0.05
Infectious AEs	Concomitant steroid use	2.00 (1.29-3.09)	<0.005
	Concomitant MTX#	2.27 (1.28-4.01)	<0.01
	Concomitant DMARDs, other than MTX#	1.43 (0.73-2.78)	0.30
	Male gender	0.69 (0.40-1.04)	0.07
dermatological AEs	Weight##	1.30 (1.08-1.55)	<0.005
	Age##	1.25 (1.03-1.52)	<0.05
	Number of previously used DMARDs	1.12 (0.98-1.28)	0.09
allergic AEs	Male gender	0.53 (0.29-0.95)	<0.05
	Number of previously used DMARDs	1.18 (1.03-1.34)	<0.05
	Age##	0.84 (0.70-1.01)	0.06
major AEs	Age##	1.36 (1.10-1.68)	<0.005
	Concomitant steroid use	1.77 (1.07-2.93)	<0.05

*stepwise backward approach with correction for TNFα blocking agent, time on therapy and centre; all variables with p<0.10 included. **dichotomized independent variables. #compared to monotherapy with TNFα blocking agents. ##For weight and age: OR per decimal increment.

DISCUSSION

This longitudinal observational study investigated the drug survival, efficacy and safety of three TNFα blocking agents, i.e. infliximab, adalimumab and etanercept, in a cohort of RA patients with active and mostly longstanding, severe RA. Furthermore, the predictive value of baseline factors for drug survival, disease activity and adverse events were analyzed. Patients were included in two Hospitals in the east of the Netherlands, which provide nearly all second-line RA treatments in an area with an estimated population size of half a million.

Observed drug survival rates are relatively low, compared to survival rates reported previously in clinical trials and biologics registries. One-year survival rates in the present study ranged between 50% for etanercept and 74% for adalimumab. In clinical trials one-year drug survival rates ranged between 73-86% for the three agents for treatment groups resembling current clinical practice [2,15-17]. Reported one-year survival rates in post-marketing observational studies vary around 65-95% [18-22]. Although in general these studies have similar baseline characteristics regarding disease duration and severity, differences exist in prescription criteria, availability of TNFα blocking agents and the use of comedication, which can contribute to encountered differences in drug survival.

In the present study drug survival rates are presented without formal comparison between the three agents. This was considered inappropriate mainly because of two reasons. Firstly, all adalimumab patients originated from RCTs, which might have a positive influence on drug-survival because of stringent exclusion criteria like comorbidity. Recently is has been shown that RA patients who are ineligible for RCTs exhibit lower response rates to TNFα blocking agents [23]. The authors comment on the 'flare design' of most recent RCTs, which includes only patients who have a high disease activity at baseline and thus a larger potential for improvement.

Secondly, the number of patients who started with etanercept was small, resulting from limited access of etanercept in the Netherlands until the end of 2003, due to scarcity of the drug.

A substantial number of patients switched from TNFα blocking agent, mostly from infliximab to etanercept. Overall, survival rates of second treatment courses were good and comparable to previous reports on switching of TNFα blocking agents [24]. In the present study the reason for discontinuation of infliximab did not seem to influence drug survival of second treatment course with etanercept. Patient numbers for other switching combinations were small and not further explored.

Disease activity over time and the response and remission rates were comparable to other observational studies [19,25-28]. Adverse events were reported frequently and led to discontinuation in 30% of the patients. The pattern of adverse events was similar to previous reports; with infections and dermatological conditions reported most frequently [2-4,15,19,29].

It is possible that therapy with TNFα blocking agents increases the risk for infections. A number of clinical trials have reported an increased risk following TNFα blocking therapy for serious infections in general [15,30,31], contrasted by studies reporting similar infection rates between patients with and without

TNFα blocking therapy [2-4]. A meta-analysis of nine trials with infliximab and adalimumab has also reported an increased risk for serious infections [32]. Substantial evidence has emerged associating TNFα blocking agents with an increased risk for tuberculosis reactivation and infections with intracellular pathogens [6,7,33-35]. More recently, large observational studies have reported an increase in serious infections in general [36,37], as well as serious skin and soft tissue infections [38].

Next to infections, the risk for malignancies remains subject to debate. A recent meta-analysis of 9 RCTs with infliximab and adalimumab showed a dose dependent increased risk in the first treatment year, compared to controls [32], although comments have been made on the choice of included trials and the unexpected low malignancy rate in control arms [39,40]. In the present study a total of ten non-skin malignancies of different origin were reported during follow-up, which does not exceed the expected malignancy risk in RA patients in general [41].

This study further investigated the predictive value of baseline and treatment characteristics on effectiveness and safety outcomes. The use of both concomitant MTX therapy and concomitant non-MTX DMARD therapy was shown to be associated with a longer drug survival time and lower disease activity over time. This is in line with previous observations. The use of concomitant MTX has been extensively studied in clinical trials, which reported overall better response rates [16,42,43]. In observational studies, higher response rates have been reported for the combination of etanercept and MTX, compared to monotherapy [25]. Similar trends were shown for infliximab, although not statistically significant [25]. Similarly, a significantly longer drug survival of TNFα blocking therapy in combination with MTX has been reported in comparison to monotherapy with TNFα blocking agents [44].

One study reported the combination of TNFα blocking therapy with MTX to result in higher response rates compared to TNFα blocking therapy with non-MTX DMARDs [25]. A more recent study confirmed that both MTX and non-MTX DMARDs predict treatment responses, with MTX being a better predictor [52]. Although the present study did not perform a direct comparison, the MTX subgroup predicted a longer drug survival time to ineffectiveness and reached higher statistical significance for the other outcomes, compared to the non-MTX DMARD subgroup.

The observation that the use of concomitant non-MTX DMARDs is associated with a better drug survival and effectiveness is interesting, particularly for patients who do not tolerate MTX. These patients might benefit from the combination of TNF blocking therapy with non-MTX DMARDs. In clinical trials only combinations with MTX have been tested. Other observational data on the comparison of concomitant non-MTX DMARDs versus monotherapy is lacking and the observations in this study need further confirmation. It must be noted that in the present study most patients on concomitant non-MTX DMARDs originated from the infliximab group.

Increased effectiveness and a decrease in number of treatment-related adverse events rate both could result from suppression of the formation of antibodies against TNFα blocking agents by using concomitant DMARDs like methotrexate, as has been shown for infliximab in Crohn's disease [45]. Formation of antibodies to the other two TNFα blocking agents occurs at very low rates [15,46].

Other factors predictive for a low disease activity over time were older age, male gender, lower baseline DAS28, no concomitant corticosteroids and less previously used DMARDs. The latter two could indicate patients with a less severe disease course. The other factors are known markers for RA disease severity [47,48]. Observational studies have reported higher remission rates in patients with a lower baseline DAS28, less previously used DMARDs, concomitant methotrexate and male gender [25,26,28].

Baseline DAS28 differs between biological registries, resulting from differences in national prescription criteria. In England a DAS28 score above 5.1 is required, whereas German and Swedish criteria hold no restriction regarding disease activity [22,25,44].

Concomitant corticosteroid use predicted adverse events in general and infections. Infections were furthermore predicted by the use of concomitant MTX. The association of infections with non-MTX DMARDs was not statistically significant. Corticosteroid and DMARD therapy has previously been associated with a higher infection rate [36,49-51]. Weight and higher age were also associated with the occurrence of adverse events, possibly by associated comorbidity. Allergic reactions were predicted by female gender and a higher number of previously used DMARDs. The latter might indicate patients with a high DMARD turnover due to toxicity or intolerability.

In conclusion, the observed survival rates of TNFα blocking agents in a Dutch cohort with longstanding, severe RA are relatively low and only a small percentage achieved remission during follow-up. For comparison of effectiveness between the different agents randomized studies are preferential. The concomitant use of DMARDs, including MTX, was found to be associated with a longer drug survival and a lower disease activity over time. For MTX, these effects were more pronounced than for non-MTX DMARDs, but this advantage was countered by an increased risk for infections, associated with concomitant MTX. The authors do not dispute the advocation of concomitant MTX therapy when prescribing a TNFα blocking agent, but further studies are needed to clarify the exact risk-benefit ratio regarding the increased risk for infections.

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CHAPTER 3

The influence of previous and concomitant leflunomide on the efficacy and safety of infliximab therapy in patients with rheumatoid arthritis; a longitudinal observational study

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Summary

Objective | To investigate the influence of previous and concomitant leflunomide on the efficacy and safety of infliximab therapy in rheumatoid arthritis (RA) and to compare it to infliximab in combination with other disease-modifying anti-rheumatic drugs.

Methods | RA patients starting infliximab therapy were prospectively followed from January 2000. Every 3 months data were collected regarding disease activity (DAS28), adverse events and treatment changes. In the primary analyses all patients were classified into a leflunomide group (LEF group) if they had used leflunomide during infliximab therapy or within 6 months prior to starting infliximab therapy, the latter because of the long half-life of leflunomide. All other patients were considered as controls (non-LEF group). Secondary drug survival analyses were performed with the LEF group consisting only of patients on active leflunomide at the start of infliximab (active LEF group).

Results | A total of 162 RA patients started infliximab therapy (57 in the LEF group, 105 in the non-LEF group). No statistically significant differences in base-line characteristics were observed between the groups. Maximum follow-up time was 46 months for both groups. No differences in drug survival, disease activity or adverse events were observed between the groups.
In both groups an increase in patients positive for antinuclear antibodies (ANA) was seen. ANA positivity at start did not predict DAS28 or the occurrence of adverse events. Secondary drug survival analyses showed no differences between the active LEF group and the non-LEF group.

Conclusion | The results indicate that the administration of infliximab after or simultaneously with leflunomide is safe and efficacious in RA patients.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that affects between 0.5 and 1% of the adult population [1]. It predominantly affects the joints, characterized by chronic synovial inflammation, and can cause severe, irreversible joint destruction and functional disability. Disease-modifying antirheumatic drugs (DMARDs) can reduce the inflammatory process and slow progression of joint destruction. Early diagnosis and initiation of DMARD treatment are important for an optimal reduction in disease progression.

Leflunomide is a relatively new DMARD, which has proven efficacy and safety in randomized controlled trials in RA [2, 3]. It is an isoxazole derivate and its active metabolite inhibits de novo pyrimidine synthesis, resulting in inhibition of T-cell proliferation. Leflunomide has a long elimination half-life of 15 to 18 days.

The development of anti-rheumatic drugs has shifted from empirically based strategies towards drugs specifically designed to target critical elements in the inflammatory process in RA. An important cytokine in RA is tumour necrosis factor alpha (TNFα) [4]. Inhibition of TNFα by monoclonal antibodies or by soluble receptors has proved to be a major advance in the treatment of RA. Two monoclonal anti-TNFα antibodies (infliximab and adalimumab) and one soluble receptor (etanercept) have proved to be efficacious in clinical trials and are currently being used in clinical practice [5–7].

Combining two or more DMARDs can enhance efficacy by either additive or synergistic effects, without a decrease in tolerability [8]. Although infliximab has proved to be efficacious as monotherapy in RA [9, 10], combining infliximab with concomitant methotrexate resulted in a sustained therapeutic response at lower infliximab doses, compared with both drugs administered as monotherapy [10]. Furthermore, the incidence of antibodies to infliximab was reduced when infliximab was administered with concomitant methotrexate, which might explain the apparent synergy between infliximab and methotrexate. In patients with Crohn's disease the development of anti-infliximab antibodies has been shown to be associated with a reduction in the duration of response and with a higher risk of infusion reactions. In addition to this, concomitant immunosuppressive treatment was associated with a reduction in antibody titres [11].

The results of Maini et al. [10] provided the rationale for the combination of infliximab and methotrexate, which has further been evaluated in clinical trials and is now the recommended strategy for infliximab therapy in RA [5, 12]. However, not all patients tolerate or respond to methotrexate, which warrants research into the combination of infliximab with other DMARDs like leflunomide.

At present three studies have been published investigating the combination of infliximab and leflunomide in RA [13–15]. All three studies report the combination to be efficacious. A marked reduction of disease activity in RA patients was reported in two studies, one 32-week open-label prospective study and one retrospective study, both with a small number of patients. However, in two studies with small patient numbers approximately half of the patients in both studies were withdrawn from therapy due to adverse events, which were in some cases severe [13, 15].

Another retrospective study in 88 RA patients showed the combination to be efficacious and well tolerated over an average of 6.6 months [14].

The reported studies lack a control group, have a limited follow-up time and two of them are retrospective. In this prospective cohort study we investigated the efficacy and safety of infliximab in RA patients with previous and concomitant use of leflunomide over a longer period and compared it with the combination of infliximab with other DMARDs.

PATIENTS AND METHODS

Patients

All RA patients starting treatment with infliximab in one academic centre were included in a prospective follow-up study starting in January 2000. To be eligible for treatment with infliximab patients had to fulfil the diagnosis of RA according to the criteria of the American College of Rheumatology [16] and were required to meet the Dutch guidelines criteria for biological therapies: moderate to high disease activity (DAS28≥3.2) and failure or intolerance of treatment with methotrexate up to 25 mg/week and at least one other DMARD in adequate dosage regimens.

Treatment

Infliximab was administered intravenously and was started according to a standard dosing regimen with a dosage of 3 mg/kg, which was rounded off to a multiple of 100 mg and was administered at the start of treatment, weeks 2, 6 (loading dose phase) and every 8 weeks thereafter. After the loading dose phase the dose or interval in individual patients could be adjusted if the response was insufficient. Guidelines for maximum infliximab dose per interval corresponded with 10 mg/kg every 8 weeks. Guidelines at the treatment centre recommended infliximab to be administered in combination with methotrexate, in accordance with general recommendations [12]. If methotrexate was ineffective or not tolerated the choice of concomitant DMARD treatment was made by the treating physician.

Evaluations

At the start of infliximab therapy the following patient characteristics were collected: age, gender, weight, duration of RA, rheumatoid factor (RF) (considered positive if RF >10 IU/ml; by enzyme-linked immunosorbent assay), antinuclear antibody (ANA; by immunofluorescence on Hep-2 cells). Previously and currently used DMARDs were recorded, as well as orally administered corticosteroids. Patients were assessed every 3 months. Assessments consisted of joint evaluations (28 joint counts for tenderness and swelling), erythrocyte sedimentation rate (ESR; Westergren method) and a patient assessment of disease activity on a visual analogue scale (VAS). Furthermore, at every visit the dosage and interval of infliximab, changes in concomitant DMARDs and systemic corticosteroids, and adverse events were recorded. ANA was measured at baseline and once a year thereafter.

Adverse events were defined as any new medical condition or worsening of a pre-existing medical condition occurring during or after treatment with infliximab and were recorded by the rheumatologist if they were considered clinically important. They were divided into minor and major events. Major events were defined as those events for which intravenous therapy or hospitalization was necessary.

In cases where infliximab therapy was discontinued the reason for discontinuation was recorded and follow-up was continued. Reasons for discontinuation were classified as discontinuation due to inefficacy, adverse events or other reasons. Disease activity was assessed using the DAS28, a composite index consisting of 28 joint counts for tender and swollen joints, the ESR and the VAS for disease activity [17, 18]. Response to treatment was evaluated using the European League Against Rheumatism (EULAR) response criteria, based on the DAS28 [19].

Statistical analysis

Patients were classified into two groups. They were classified into the leflunomide group (LEF group) if they were using leflunomide during infliximab treatment or if they had used leflunomide within the last 6 months prior to starting infliximab therapy, the latter because of the long half-life of leflunomide. All other patients were considered in the control group (non-LEF group). These groups were compared for baseline characteristics, drug survival, adverse events, reason for discontinuation, DAS28 over time and ANA status. Secondary analyses were performed with the LEF group consisting only of patients on active leflunomide therapy at the start of infliximab (active LEF group). All other patients were considered as controls. Baseline characteristics were compared and drug survival analyses were repeated. Furthermore, patients on infliximab monotherapy were compared with patients on infliximab-DMARD combinations for differences in baseline characteristics, adverse events and ANA status.

Differences in baseline characteristics between groups were compared by chi-square tests for dichotomous variables and Student's t-tests for continuous variables. Life table analysis was performed to compare drug survival on infliximab between groups with 1 January 2004 as the date of censoring. Separate drug survival analyses were performed for inefficacy and for adverse events as reasons for discontinuation. To correct for possible differences in baseline characteristics between the groups Cox regression analysis was used. In addition, the same analyses were repeated for the active LEF group.

Adverse events and reasons for discontinuing infliximab therapy were compared between the treatment groups. The DAS28 over time was compared between groups by longitudinal regression analysis using generalized estimating equations (GEE). Differences in baseline characteristics between the groups were corrected for. The exchangeable correlation structure was used and the identity link function and the Gaussian variance model were applied. Percentages of response were calculated for the groups at 3, 6, 12, 18 and 24 months.

Differences between groups in ANA status at start and during follow-up were compared by chi-square tests. Relative risks of developing adverse events over the first year of follow-up were calculated for ANA-positive patients at baseline as opposed to

ANA-negative patients at baseline for both treatment groups, and for conversion to ANA positivity as opposed to patients who remained ANA negative during infliximab therapy for both treatment groups. The DAS28 over time was compared overall between patients who were ANA positive and ANA negative at the start of infliximab using GEE with the exchangeable correlation structure. Analyses were performed using SAS statistical software (version 8.0, SAS Institute Inc., USA), and SPSS statistical software (version 11.0, SPSS Inc., USA).

Ethical approval was obtained from the Ethical Committee of the University Medical Centre St Radboud for the observational study. Patient informed consent was obtained verbally; no written informed consent was required.

RESULTS

Since January 2000 a total of 162 RA patients started infliximab therapy, of whom 57 used leflunomide during infliximab therapy or in the 6 months prior to starting infliximab therapy. The characteristics of these patients are shown in table 3.1. Although some small differences in baseline characteristics were seen, none of them were statistically significant.

Table 3.1: Baseline characteristics at start of infliximab therapy

	LEF group (n=57)	NON-LEF group (n=105)	P-value
Age in years, mean (SD)	54.2 (14.3)	58.1 (11.5)	0.08
Female sex, n (%)	41 (71.9)	74 (70.5)	0.87
Weight in kg, mean (SD)	74.2 (14.2)	74.1 (12.3)	0.97
Duration of disease in yr, median (range)	8.7 (1.2-38.7)	11.0 (1.2-44.9)	0.23
RF positivity, n (%)	52 (91.2)	86 (81.9)	0.11
ANA positivity, n (%)	24 (47.1)*	38 (38.0)*	0.24
Disease activity score (DAS28), mean (SD)	5.7 (1.0)	5.9 (1.1)	0.47
No. of prior DMARDs, median (range)	4 (1-9)	3 (2-8)	0.12
No. of concomitant DMARDs, n (%)			
0	11 (19.3)	22 (21.0)	
1	40 (70.2)	66 (62.9)	
2	6 (10.5)	16 (15.1)	
3	0 (0.0)	1 (1.0)	
Concomitant prednisone at baseline, n (%)	18 (31.6)	27 (25.7)	0.52
Prednisone dose in mg/d at baseline, median (range)	7.5 (5-20)	10 (5-30)	0.22

*ANA at baseline available for 51 and 100 patients in the LEF group respectively NON-LEF group

DMARD treatment

The LEF group consisted of 33 patients (58%) who used leflunomide at the start of infliximab therapy and 24 patients (42%) who had stopped leflunomide therapy in the last 6 months before starting infliximab therapy (median 3.7 months (range 0.0-6.0) before starting infliximab). Thirteen patients had stopped leflunomide because of adverse events, seven for inefficacy and four for both adverse events and inefficacy. Of these 24 patients 11 had started infliximab as monotherapy, seven used methotrexate, five used azathioprine and one used sulphasalazine as concomitant therapy. Of the 33 patients on infliximab and leflunomide five also used methotrexate and one also used hydroxychloroquine. Oral corticosteroids were used by five patients (46%) on infliximab monotherapy and by 13 patients (28%) on infliximab and concomitant DMARDs in the LEF group. No statistically significant differences in baseline characteristics were found between patients on active leflunomide therapy and patients who had stopped leflunomide in the 6 months prior to start of infliximab.

The median duration of leflunomide treatment was 11 months (range 0-66 months) with a median dose of 20 mg/day (range 10-30 mg/day). In the 33 patients who used leflunomide during infliximab therapy 12 (36%) stopped leflunomide during infliximab therapy (five for inefficacy and seven for adverse events) and three (9%) stopped leflunomide after infliximab therapy was discontinued (three adverse events). The median duration of leflunomide treatment during infliximab was 9 months (range 2-32 months).

In the non-LEF group 22 patients used infliximab as monotherapy. Concomitantly used DMARDs were methotrexate (n=62), sulphasalazine (n=19) and azathioprine (n=12), hydroxychloroquine (n=1) and parenteral gold (n=1). Oral corticosteroids were used by four patients (18%) on infliximab monotherapy and by 23 patients (24%) on infliximab and concomitant DMARDs in the non-LEF group.

Infliximab therapy

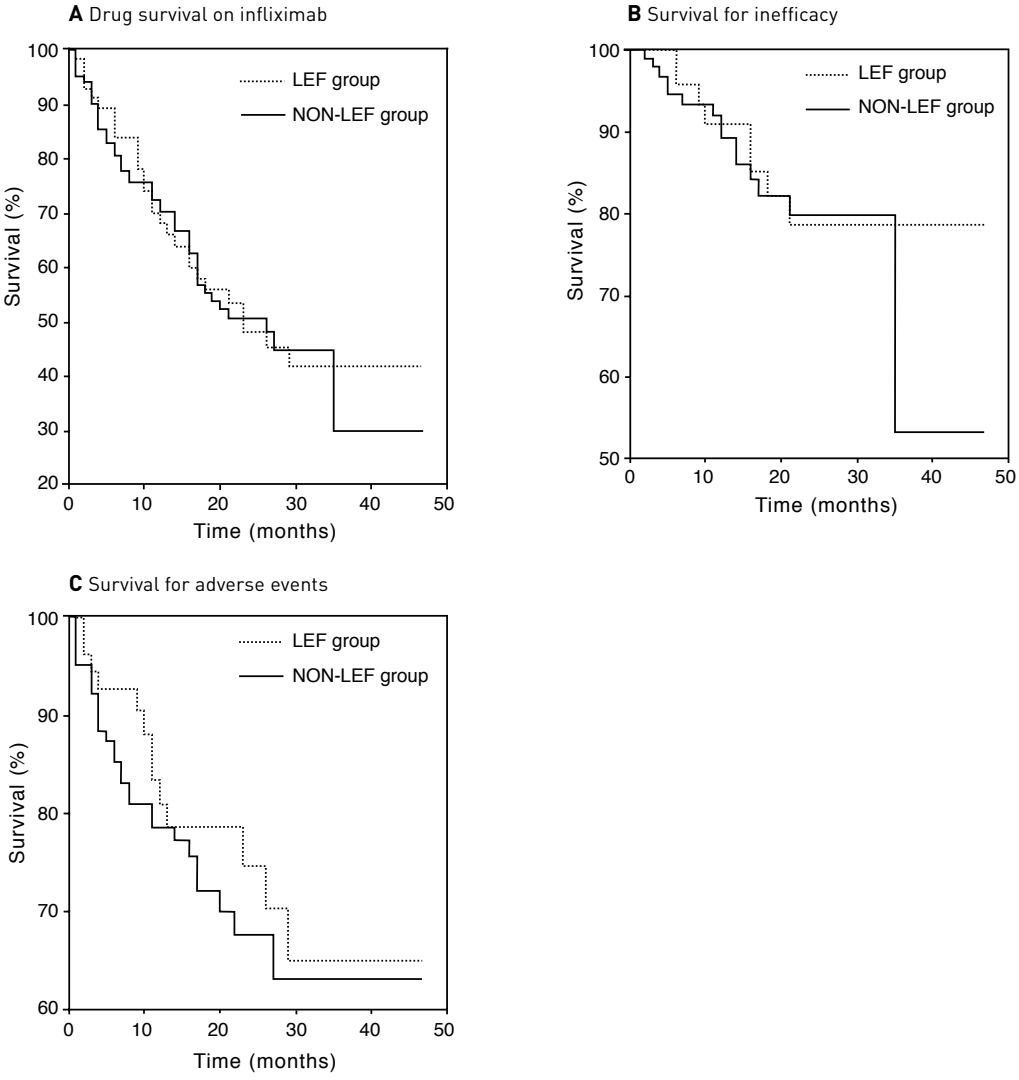
Mean infliximab dose at the start of therapy was 253 mg in the LEF group and 257 mg in the non-LEF group. After 6 months of infliximab therapy two dosage increases and no interval reductions were seen in the LEF group, compared with seven dosage increases and four interval reductions in the non-LEF group. After 12 months of therapy 12 dosage increases and one interval reduction were seen in the LEF group, compared with 10 dosage increases and five interval reductions in the non-LEF group. Mean doses at 6 and 12 months were 262 mg and 317 mg every 8 weeks in the LEF group, and were 268 and 300mg every 8 weeks in the non-LEF group. Patients' body weight did not differ between the two groups.

Drug survival

Maximum follow-up time was 46 months in both groups. No difference in survival on drug was found between the two groups, as shown in figure 3.1A. Median survival time was 23 months in the LEF group and 25 months in the non-LEF group. After correction for differences in baseline variables also no differences in drug survival were seen. In separate drug survival analyses no differences between the two groups

could be shown for discontinuation of infliximab therapy due to inefficacy and due to adverse events (figures 3.1B and 3.1C). In secondary analyses drug survival was compared between patients on active leflunomide treatment at the start of infliximab (active LEF group) and controls. No significant differences between the two groups were found, also after correction for differences in baseline characteristics.

Figure 3.1. Drug survival on infliximab.



(A) Drug survival on infliximab for the LEF group and the non-LEF group. (B) Survival to drug discontinuation for inefficacy. (C) Survival to drug discontinuation for adverse events.

Disease activity

Disease activity over time, as measured by the DAS28, is shown in figure 3.2. No statistically significant differences in disease activity over time were found between the groups, also after correction for possible confounding baseline differences. The response percentages for both groups at each time point are shown in figure 3.3. In the LEF group between 67 and 77% of the patients showed a response at any point in time, and in 14 to 44% of the patients the response was good, according to the EULAR criteria for response. In the non-LEF group between 63 and 75% of the patients showed a response at any point in time, and in 21 to 32% of the patients the response was good.

Figure 3.2. Disease activity (DAS28) over time

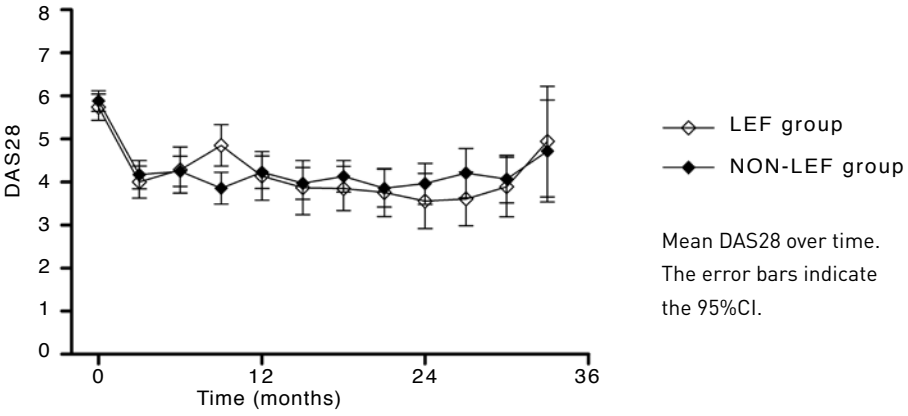
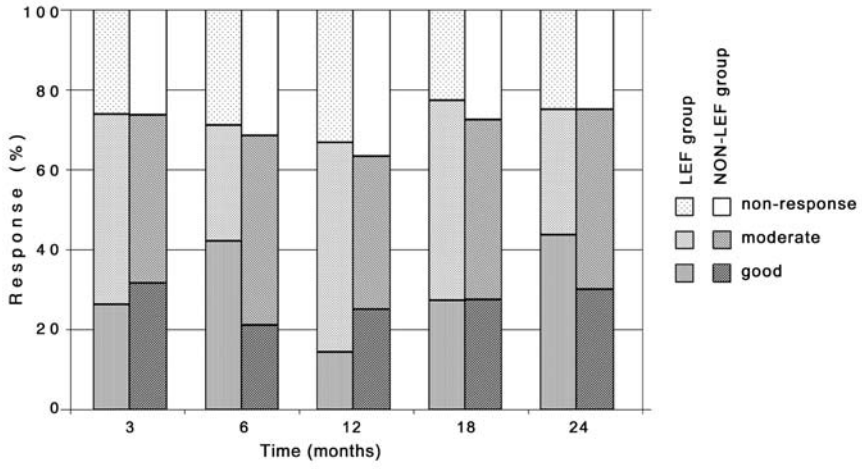


Figure 3.3. Response to treatment over time



Reasons for discontinuation

Table 3.2 shows the reasons for discontinuation of infliximab. In both groups the major reasons for discontinuation were adverse events. Inefficacy as a reason for discontinuation was reported equally in both groups. A small number of patients discontinued infliximab because of other reasons, like a desire for pregnancy, increased availability of etanercept and patient's initiative.

Table 3.2. Reasons for discontinuation of infliximab

Reasons for discontinuation, N (%)	LEF group (N=57)	NON-LEF group (N=105)
Inefficacy	10 (17.5)	16 (15.2)
Adverse events	14 (24.6)	29 (27.6)
Other	4 (7.0)	4 (3.8)
All reasons	28 (49.1)	49 (46.6)

Adverse events

The adverse events encountered are listed in table 3. In the LEF group 32 patients (56%) reported a total of 65 adverse events, of which seven were major events. In the non-LEF group 61 patients (58%) reported 103 adverse events, of which 14 were reported as major. Major infection was reported once in the LEF group and nine times in the non-LEF group. In the LEF group one patient was hospitalized for a pneumonia and sepsis with *Streptococcus pneumoniae*. The major infections reported in the non-LEF group were four pneumonias (one pulmonary tuberculosis), one septic oligoarthritis (*Staphylococcus aureus*), one bacterial discitis with urosepsis (*Escherichia coli*), one perforated appendicitis, one infected leg ulcer and one patient with infected osteosynthetic materials. No malignancies were reported in the LEF group and two malignancies were reported in the non-LEF group. One breast carcinoma with metastasis occurred during infliximab. Also, one leukaemia reaction with leucopenia was reported. Initially, a spontaneous recovery was seen after stopping infliximab, but 2 yr later the patient developed acute myeloid leukaemia. In the LEF group six other serious adverse events were reported, as well as three in the non-LEF group (see table 3.3).

The most frequent minor adverse events reported in both groups were infections, infusion reactions, allergic reactions and dermatological conditions. A systemic lupus erythematosus (SLE)-like syndrome was reported in three patients in the LEF group only (two major adverse events). One major and five minor neurological events were reported, all in the non-LEF group. They included headache (n=2), one radicular syndrome (major adverse event), one peripheral nerve palsy, one optic neuritis and one demyelinating disease. The latter presented with peripheral nerve palsy and white matter lesions.

Table 3.3. Adverse events

	LEF group (N=57)	NON-LEF group (N=105)
No. (%) of patients with adverse events	32 (56)	61 (58)
No. (%) of adverse events*		
Major adverse events	7 (10.7)	14 (13.6)
Infections	1 (1.5)	9 (8.7)
Myocardial infarction	2 (3.1)	1 (1.0)
SLE-like syndrome	2 (3.1)	-
Polymyositis	-	1 (1.0)
Malignancy	-	2 (1.9)
Myalgia	1 (1.5)	-
Fatigue	1 (1.5)	-
Spinal stenosis	-	1 (1.0)
Minor adverse events	58 (89.3)	89 (86.4)
Infections	20 (30.8)	33 (32)
Allergic/infusion reactions	17 (26.2)	26 (25.2)
Dermatological conditions	12 (18.5)	12 (11.7)
Constitutional symptoms	2 (3.1)	1 (1.0)
Cardiovascular	2 (3.1)	3 (2.9)
Neurological	-	5 (4.9)
Laboratory abnormalities	2 (3.1)	3 (2.9)
SLE-like syndrome	1 (1.5)	-
Gastrointestinal	-	3 (2.9)
Pulmonary	-	2 (1.9)
Diabetes mellitus	1 (1.5)	1 (1.0)
Gingival hyperplasia	1 (1.5)	-
Total adverse events	65 (100)	103 (100)

*Percentage of total adverse events per group

Anti-nuclear antibodies

ANA status at the start of infliximab therapy was available for 51 patients (90%) in the LEF group and 100 patients (95%) in the non-LEF group. ANA status during follow-up was available for 46 patients (81%) in the LEF group and for 79 patients (75%) in the non-LEF group. In the LEF group 24 patients (47%) were ANA positive at start and in the non-LEF group 38 patients (38%) were ANA positive at start of infliximab therapy.

Of the patients who were ANA negative at the start 70% in the LEF group and 65% in the non-LEF group converted to ANA positivity during infliximab therapy. Of these patients 70 and 82% respectively remained ANA positive throughout infliximab therapy in the LEF group and non-LEF group respectively. Of the patients who were ANA positive at the start 4% in the LEF group and 11% in the non-LEF group con-

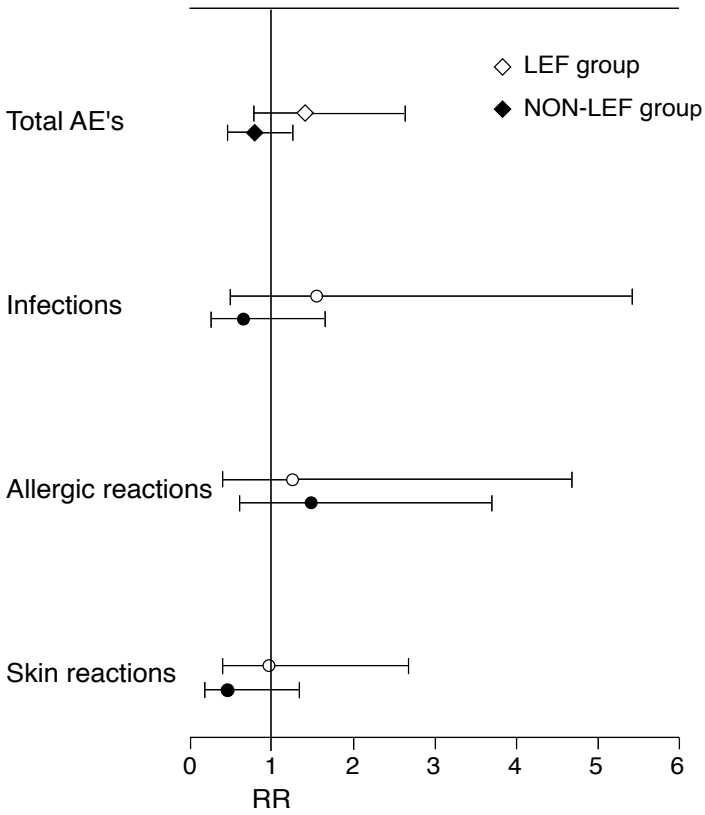
verted to ANA negative. The differences between the two groups in number of ANA-positive patients at the start and during follow-up were not statistically significant (P=0.29, respectively P=0.18).

Overall, no differences in DAS28 over time were found between patients who were ANA positive and ANA negative at the start.

The estimated relative risks for ANA positivity at baseline of developing adverse events over the first year of follow-up were calculated and are shown in figure 3.4. For both treatment groups ANA positivity at baseline did not increase or decrease the risk for adverse events.

Furthermore, patients who converted to ANA positivity did not have a higher relative risk (RR) for adverse events [RR=0.83 (95%CI=0.29–2.37) in the LEF group, RR=1.32 (95%CI=0.74–2.35) in the non-LEF group].

Figure 3.4. Estimated relative risks of developing adverse events in the first year of follow-up for ANA positivity at start of infliximab.



Infliximab monotherapy

A total of 33 out of 162 patients started infliximab without concomitant treatment with DMARDs, equally distributed between the LEF group and the non-LEF group (see results, DMARD treatment). No statistically significant differences were found in baseline characteristics, except for the mean prior number of DMARDs [4.7 (SD=1.7) in patients on monotherapy versus 3.9 (SD=17) in patients on concomitant DMARDs, P=0.03].

Forty-one adverse events (six major adverse events, were recorded in 20 of 33 patients (61%) on monotherapy, compared with 130 (15 major) in 73 of 129 (57%) patients on concomitant treatment with DMARDs. No statistically significant differences were found in the number of patients experiencing adverse events (P=0.67) or in the number of adverse events per patient (P=0.56).

ANA conversion from negative to positive occurred in 77% of the patients on monotherapy and in 60% of the patients on concomitant treatment with DMARDs (P=0.22). Conversion from positive to negative occurred in 9% of the patients on monotherapy and in 8% of the patients on concomitant DMARDs (P=0.96).

DISCUSSION

In this study the safety and efficacy of infliximab was investigated in patients with RA, who previously or concomitantly used leflunomide therapy, compared with patients treated with infliximab, either as monotherapy or in combination with other DMARDs. The results indicate that previous or concomitant leflunomide therapy in combination with infliximab is safe and effective for the treatment of RA patients in daily clinical practice.

We investigated the clinical consequences, in terms of survival on drug, efficacy and safety, of a possible interaction between infliximab and leflunomide. An interaction can take place in the period of active use of both drugs in combination, as well as during the elimination phase after withdrawal of one of the drugs. The active metabolite of leflunomide (A771726) has a relative long half-life of 15 to 18 days in RA patients [2], which results from low hepatic clearance and enterohepatic cycling. The standard deviation is 9 days (in a group of RA patients who received 25 mg/day in a phase II study) [20], indicating large differences in the duration of the elimination phase between individuals. In our analysis we included patients who stopped leflunomide in the 6 months prior to the start of infliximab into the LEF group in the study. Six months is approximately 10 times the mean halflife of A771726, after which only 0.1% of the original plasma concentration is present. To investigate the effect of the chosen group definition on the results a second analysis was performed including only patients who used leflunomide during infliximab therapy in the leflunomide group.

In this study the two treatment groups showed no statistically significant differences in baseline characteristics, although patients in the LEF group were more often RF positive and had used more DMARDs before starting infliximab therapy, both indicating a more severe course of the disease. The survival on drug was

comparable between both groups, with a median survival time of approximately 2 yr. Also, in the secondary analyses drug survival was comparable between groups.

The disease activity was comparable between the groups. In both groups the mean DAS28 showed a marked decrease after onset of infliximab therapy, which then remained more or less stable over the course of follow-up. Also, the response percentages observed were comparable for both groups. Both treatment groups showed variation in response over time, but overall no consequent pattern was seen.

The effects on disease activity in the LEF group are similar to the effects of a 32-week open-label study with 20 RA patients [15]. All patients first started on leflunomide and shortly thereafter on infliximab. At start these patients had a very high disease activity, probably due to a washout period. The mean DAS28 dropped from 7.18 at the start to 5.18 at week 4 and remained between 3.85 and 4.85 throughout the study.

In a retrospective multicentre study with 88 RA patients who had received leflunomide in combination with infliximab, Hansen et al. [14] also showed a marked decrease in disease activity parameters. Most patients had used leflunomide for several months before starting infliximab, as in our study. The authors did not present response measures because the data set was incomplete.

The reasons for discontinuation of infliximab reported in the present study were more often adverse events than inefficacy. These findings are in line with previous reports, although drug survival rates differ. Kiely et al. [15] reported 12 of 20 patients to have stopped combination therapy before 32 weeks because of adverse events, which consisted of skin reactions, infusion reactions, respiratory infections, diarrhoea, elevated liver enzymes, hypertension and mucosal ulceration, and were in some cases severe. Godinho et al. [13] retrospectively assessed the safety of the combination of leflunomide and infliximab in 17 RA patients. Adverse events were reported in 13 (76%) patients. Eight patients (47%) stopped the combination therapy because they experienced adverse events before the fifth infusion. The adverse events that led to discontinuation included heart failure, hypertension with thoracic pain, eczematous patches and neutropenia. In all three patients with neutropenia white cell counts returned to normal after stopping leflunomide.

The retrospective data collection in one study and the small number of patients in both previous studies makes interpretation difficult. Furthermore, in the study by Kiely et al. patients started both drugs within a short period of time [15]. This could have contributed to the high number of adverse events, compared with the present study in which most patients had started leflunomide in the months or years before infliximab. They either tolerated the drug or had stopped using it in the 6 months prior to start of infliximab. It must be noted that in the present study adverse events were only reported if they were considered as clinically important by the treating rheumatologist.

In the study by Hansen et al. [14] 88 patients received infliximab in combination with leflunomide over an average of 6.6 months. Ten patients (11%) had discontinued infliximab therapy during the follow-up period, six (7%) because of adverse events. These findings are more in line with the survival rates in the present study than the studies reported above. In the present study 16% had discontinued infliximab after 7 months, as shown in figure 3.1A.

Major and minor adverse events were reported in equal percentages of patients in the two treatment groups, but the number of adverse events per patient was slightly higher in the LEF group. The most common minor adverse events were skin reactions, infusion reactions and infections and were reported slightly more frequently in the LEF group. To our knowledge most adverse events in the present study have been reported previously during infliximab therapy [5, 10], with the exception of diabetes mellitus and gingival hyperplasia.

ANA are commonly found in RA patients and an increase in ANA-positive patients during infliximab treatment has been observed [13, 15, 21–23]. In previous reports no association of ANA has been found with the rate of discontinuation [21], the occurrence of adverse events [13] or loss of efficacy of infliximab [23].

In the present study no differences in DAS28 over time were found between patients who were ANA positive and ANA negative at the start of infliximab. Also, ANA positivity at baseline and conversion to ANA positivity during infliximab treatment were not associated with an increased risk for adverse events in either treatment group. For ANA conversion patient numbers were small and interpretation needs to be made with caution.

Combining DMARDs and biological therapies could increase treatment options and enhance treatment effect in clinical practice. The combination of infliximab with DMARDs other than methotrexate is of special interest, firstly because infliximab is an important new therapeutic option in RA treatment and secondly because monotherapy is not widely accepted as an option because of the possible problem of immunogenicity. Thirdly, not all patients tolerate or respond to methotrexate, which is the only DMARD investigated in combination with infliximab in randomized controlled trials.

The present study shows that previous or concomitant treatment with leflunomide does not decrease the efficacy of infliximab therapy in RA patients. Furthermore, the safety data presented in this study are reassuring and show previous or concomitant treatment with leflunomide in combination with infliximab to be safe and well tolerated. The results indicate that infliximab is safe and efficacious after previous treatment with leflunomide and that the combination of infliximab and leflunomide is a valuable therapeutic option in RA.

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CHAPTER 4

Titration of infliximab treatment in rheumatoid arthritis patients based on response patterns

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Summary

Objectives | To observe the course of the disease activity in rheumatoid arthritis (RA) patients treated with the standard infliximab dosing regimen and to adjust treatment guided by the pattern of disease activity.

Methods | All RA patients starting infliximab treatment were included and observed for at least 37 weeks. At infusion 4 (week 14), European League Against Rheumatism response was assessed. In moderate responders the dose was unchanged and the disease activity was carefully observed. In case of stable disease activity, the dose was increased at infusion 5 (week 22). In case of a temporary response the interval was reduced. Paired t-testing was applied to the disease activity score with 28-joint counts (DAS28) at week 22 and study endpoint.

Results | A total of 76 patients were included. Response after 14 weeks: good 22 (29%) patients, moderate 26 (34%) patients, and non-response in 21 patients. Seven patients (9%) dropped out before week 14 due to adverse events (5) or patients' initiative (2). In patients with moderate response, the following disease course between infusion 4 and 5 was observed: improvement to good response 6, temporary response 6, stable disease activity 6, drop out 8. In moderate responders, interval reduction and dose increase resulted in a decrease in mean DAS28 from 5.1 to 3.6 [P=0.005, mean interval 5.6 weeks, mean infliximab dose 4.8 mg/kg/8 week (endpoint)] and from 4.1 to 3.6 [P=0.04, mean infliximab dose 7.3 mg/kg/8 week (endpoint)], respectively.

Conclusion | Three different patterns of disease activity were observed in moderate responders after 14 weeks of infliximab treatment, i.e. further improvement, no change in disease activity or a temporary response. Both interval reduction and dose increase significantly reduced disease activity, however, with different mean infliximab dosages. In good responders the response was often sustained over follow-up, whereas non-responders showed modest or no improvement despite dose adjustments.

INTRODUCTION

Infliximab, a chimeric monoclonal antibody directed against tumour necrosis factor-α (TNFα), is efficacious in rheumatoid arthritis (RA) [1]. The recommended starting dose is 3 mg/kg, administered by intravenous infusion at weeks 0, 2 and 6 and every 8 weeks thereafter [2]. However, this dosage regimen seems to be insufficient in a subset of RA patients. In clinical practice, both dose increase (up to 10 mg/kg every 8 weeks) and interval reduction (to minimal 4 weeks) are being used [3–5].

At present no clear recommendations exist regarding the strategy that should be used in case of moderate or non-response. Previous studies have shown that dose titration as well as interval titration with TNFα blocking agents can be used to achieve disease activity improvement in individual RA patients [6, 7]. A large variation in dosage as well as in time interval was shown in these studies in order to maintain low disease activity.

In this open-label study, we evaluated the course of the disease activity with a disease activity score with 28-joint counts (DAS28) and the European League Against Rheumatism (EULAR) response criteria in RA patients starting infliximab treatment. In addition to this, the effect of dose increase and interval reduction on the disease activity was investigated in those patients who had a moderate response after 22 weeks. The decision to increase the dose or to reduce the interval was based on observations of the course of the DAS28 in the period between the 4th and 5th infusion.

PATIENTS AND METHODS

Study design

All consecutive patients with RA, according to the American College of Rheumatology (ACR) criteria [8], starting infliximab therapy between April 2002 and January 2004, were prospectively followed. According to the Dutch guidelines for biological therapies, infliximab was started in RA patients with active disease (DAS28 ≥ 3.2) after treatment failure of at least two disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate up to 25 mg/week.

Evaluations

At the start of infliximab treatment, the following data were collected: age, sex, disease duration, rheumatoid factor (RF) positivity, the number of previously used DMARDs and the use of concomitant DMARDs and systemic corticosteroids. Follow-up visits took place on each infusion day just prior to infusion; in moderate responders, additional visits were made at weeks 18 and 20 (between the 4th and 5th infusion). Disease activity was assessed at each visit, using the DAS28, which is a validated composite score of the erythrocyte sedimentation rate tender and swollen joint count and the visual analogue scale general health of the patient [9]. Treatment response was evaluated at week 14 (4th infusion), using the EULAR response criteria [10], dividing patients into good, moderate and non-responders. All patients were

followed for 38 weeks of infliximab treatment (37–41 weeks in patients who received an interval reduction). Reasons for discontinuation were recorded, if appropriate.

Treatment

Infliximab was started in the standard dosing regimen of 3 mg/kg body weight with infusions at week 0, 2, 6 and every 8 weeks thereafter. Doses were rounded off to 200 mg for patients with a body weight <70 kg and to 300 mg for patients of 70 kg or more.

Good responders. Infliximab was continued at 8-week intervals until week 38. If disease activity increased during follow-up, dose increases were possible after week 22.

Moderate responders. The dose was kept stable between week 14 (4th infusion) and week 22 (5th infusion). At week 22, infliximab treatment was tailored according to the course of the disease activity between weeks 14 and 22. Moderate responders with a stable disease activity in this period were assigned to the dose increase group in which the dose was increased to 6 mg/kg every 8 weeks. Prior to every upcoming infusion, disease activity was re-evaluated. If the DAS28 remained ≥ 3.2, the dose was further increased to 10 mg/kg/8 week.

According to the flare criteria [6], patients received an interval reduction if the DAS28 showed, after an initial improvement, an increase of more than 1.2 points between weeks 14 and 22, or an increase of more than 0.6 points up to a value above 5.1. (figure 4.1B). The new interval was calculated by subtracting 1 week from the week in which the patient flared. If the patient flared again despite the interval reduction, the interval was further reduced stepwise to a minimum of 4 weeks. To be eligible for the tailored treatment protocol, patients were not allowed to have received changes in concomitant DMARDs within 6 weeks prior to baseline or changes in corticosteroids (oral or intramuscular) after week 8 of baseline until the end of the study.

Non-responders. The dose was increased to 6 mg/kg/8 week at week 14. Dose increases up to 10 mg/kg/8 week were possible in case of a persisting non-response. Patients who stopped before week 38 because of inefficacy were considered non-responders.

Statistical analysis

Normal distribution of the DAS28 was verified (Shapiro–Wilk's statistic). Two-sided paired t-testing (P-value <0.05) was applied to the DAS28 at week 22 and at the end of the study for moderate responders in the dose increase group and in the interval reduction group. Analyses were done on an intention-to-treat basis. SPSS software was used for statistical analyses (version 11.0, SPSS inc., USA).

Figure 4.1. Disease activity (DAS28) over time

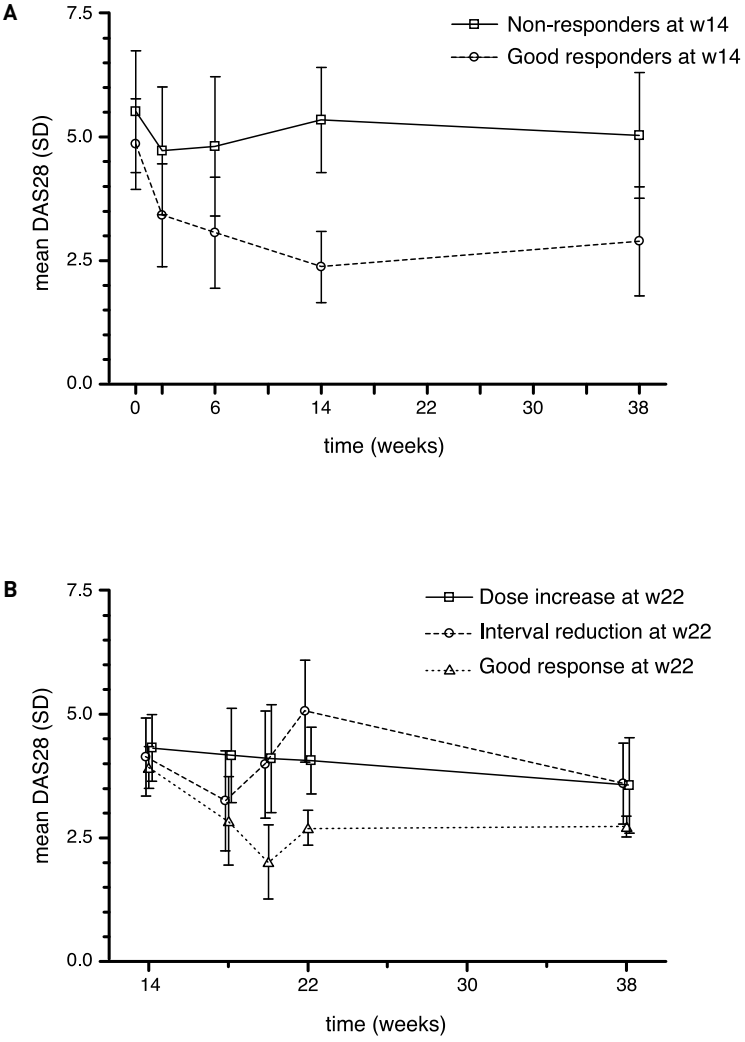


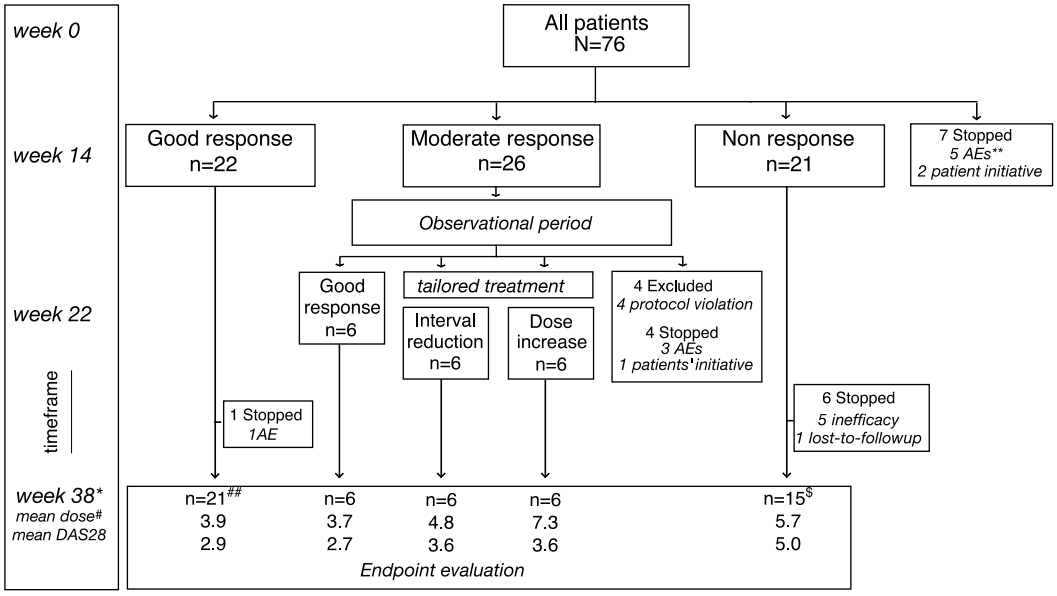
Figure 4.1A: Mean DAS28 (SD) over time in patients with a good response and with a non-response at week 14. Figure 4.1B: Mean DAS28 (SD) over time in patients with a moderate response at week 14.

RESULTS

A total of 76 RA patients started infliximab. Baseline characteristics were: mean age at start 55.7 yr [standard deviation (SD) 13.2], male sex 34%, median disease duration 7.4 yr (range 1.0–35.8), RF positivity 82%, mean DAS28 5.4 (SD 1.1) and median number of prior used DMARDs three (range 2–8).

At the start of infliximab treatment, 67 patients (88%) used concomitant DMARDs, 55 (72%) used one DMARD and 12 (16%) used two DMARDs. Nineteen patients (25%) used prednisolone with a median dose of 8 mg/day (range 5–15). Seven (9%) patients were on infliximab monotherapy. Figure 2 shows the study flowchart with patient distribution.

Figure 4.2. Study flowchart with patient distribution



*Endpoint between week 37 and 41 for patients receiving interval reduction. **AEs, adverse events. #Mean infliximab dose calculated per eight weeks. ##Three of 21 patients received a dose increase between weeks 22 and 38. $All 15 patients received a dose increase, three patients two dose increases and three patients interval reduction.

Response to treatment at week 14

Twenty-two patients (29%) were good responders, 26 patients (34%) moderate responders and 21 patients (28%) were non-responders. Seven patients (9%) had stopped infliximab before week 14 [5 adverse events (AEs) and 2 patients' initiative, see figure 4.2].

Good responders

Twenty-one out of 22 were still on infliximab at the end of the study. Thirteen patients (59%) had remained in their good-responder status, seven patients (32%) had a moderate response and one patient (5%) had changed into a non-responder, compared with baseline disease activity. One patient had discontinued infliximab because of an AE. Three patients had received a dose increase after week 14. No interval reductions were applied. The mean DAS28 was 4.9 (SD 0.9), 2.4 (SD 0.7) and 2.9 (SD 1.1) at baseline, week 14 and week 38 (39% change to baseline DAS28), respectively (figure 4.1A). The mean infliximab dose had increased from 3.6 mg/kg/8 week at the start to 3.9 mg/kg/8 week.

Concomitant therapy changes after week 14 in good responders. Concomitant DMARD therapy was reduced in four patients and stopped in three (one low disease activity and two AE). Oral prednisolone (median 6.5 mg/day at start, range 5–10) was reduced in three patients and stopped in one due to low disease activity. One patient received an intramuscular corticosteroid injection after an increase in disease activity.

Moderate responders

In the patients who were classified as moderate responders at week 14, three different patterns of disease activity were observed in the period between week 14 and 22: (A) improvement to good response (n=6), (B) stable pattern of disease activity (n=6) and (C) flare of disease activity after an initial improvement (n=6) (figure 4.2). Eight patients dropped out between weeks 14 and 22: four protocol violation, three AEs, one patient initiative. In the remaining moderate responders, concomitant DMARD treatment (used by 15 patients) and prednisolone treatment (used by two patients, median 8 mg/day, range 6-10) were kept stable throughout the study.

In patients who flared, the interval was reduced to 7 (n=1), 6 (n=3) and 5 weeks (n=3). One patient flared in the next interval and received a further interval reduction from 6 to 5 weeks. After reducing the interval, the DAS28 decreased by 1.5 (mean, SD 0.7). The mean DAS28 was 5.1 (SD 1.0) at week 22 and 3.6 (SD 0.8) at the endpoint (P=0.005, compared with week 22). The mean interval was 5.6 weeks and the mean infliximab dose increased from 3.8 mg/kg/8 week at week 22 to 4.8 mg/kg/8 week at the endpoint.

In patients with a stable disease activity pattern, the dose was increased to 6 mg/kg/8 week at week 22. Two patients received a further dose increase to 10 mg/kg/8 week at week 30. The mean DAS28 was 4.1 (SD 0.7) at week 22 and 3.6 (SD 1.0) at the endpoint (P=0.04, compared with week 22). The mean infliximab dose had increased from 4.0 mg/kg/8 week at week 22 to 7.3 mg/kg/8 week at the endpoint.

Patients who improved to good responders at week 22 remained good responders. The mean DAS28 was 2.7 (SD 0.4) at week 22 and 2.7 (SD 0.2) at week 38. No dose or interval adjustments were applied. The mean infliximab dose was 3.7 mg/kg/8 week.

Non-responders

At week 14, one patient was lost to follow-up and two patients stopped treatment due to inefficacy. All other patients received a dose increase. At the endpoint, 15 patients had continued treatment and three patients had stopped due to inefficacy. Four patients had received a further dose increase and three patients had received an interval reduction. Five patients improved to moderate responders and 10 patients remained non-responders.

The DAS28 decreased by 0.4 (median, range -1.6 to 3.3). The mean DAS28 was 5.5 (SD 1.2), 5.3 (SD 1.4) and 5.0 (SD 1.3) at baseline, week 14 and week 38 (9% change to baseline DAS28), respectively figure 4.1A). The mean infliximab dose had increased from 3.4 mg/kg at the start to 5.7 mg/kg/8 week. Concomitant therapy changes after week 14 in non-responders. Concomitant DMARD therapy was increased in two but, reduced in two patients because of side-effects and stopped in four (three inefficacy and one AE). Prednisolone dose (median 10 mg/day at start, range 5-15) was increased in two patients and started in one patient. Four patients received an intramuscular corticosteroid injection after week 14.

End of study evaluations

Overall, at the study endpoint, 25 patients (33%) were good responders, 19 (25%) moderate and 18 (24%) were nonresponders (including five patients who had stopped due to inefficacy). Nine patients (12%) had stopped due to AEs and five (7%) due to other reasons. The AEs as reason for discontinuation were: two infusion reactions (patients on concomitant hydroxychloroquine and azathioprine, respectively), one drug-induced lupus erythematosus after 7 weeks of infliximab monotherapy [characterized by anti-nuclear antibodies (ANA) and anti double-stranded DNA (anti-ds-DNA) positivity, anaemia, thrombocytopaenia, polyarthritis and proteinuria), one urosepsis with suspicion of bacterial discitis, one radicular syndrome, one wound abscess, one papular skin eruption, one diarrhoea and one hypertension. Two of these patients were hospitalized (urosepsis and radicular syndrome).

DISCUSSION

In the present study, disease activity was closely observed in RA patients starting infliximab treatment. After 14 weeks of treatment, 29% had a good response, 34% had a moderate response, 28% were non-responders and 9% had stopped treatment. In most good responders the response was sustained over follow-up. In moderate responders, remarkably three different patterns of disease activity were observed between the 4th and 5th infusion: (A) further improvement to good response, (B) a constant moderate pattern of disease activity and (C) a flare of disease activity after an initial improvement. Non-responders showed modest or no improvement despite

dose adjustments. The different response patterns seen in moderate responders might be explained by individual variations in pharmacokinetics of infliximab [11]. Serum trough concentrations of infliximab show large differences between individual patients and correlate with response [11, 12]. It has been hypothesized that patients who flare during the 8-weekly interval receive adequate therapeutic dosages, but eliminate infliximab more rapidly from the bloodstream than do patients with a constant response pattern.

Treatment adjustments of infliximab occur frequently in daily clinical practice [3, 4]. The rationale for dose increases up to 10 mg/kg/8 week was provided by the ATTRACT trial, in which part of the outcome measurements showed a dose-response relationship [1]. The pharmacokinetic modelling study of the ATTRACT data showed that interval reduction might be more effective in raising serum infliximab concentrations than dose increase [11]. At present, no randomized controlled trial has been conducted to investigate the benefit of these two options.

In the present open-label study, infliximab treatment was tailored, guided by the observed disease activity patterns, in patients with a moderate response after 14 weeks of treatment in an open-label trial setting. Interval reduction and dose increase, both resulted in a statistically significant reduction in disease activity (despite the small number of patients receiving the adjustments). The infliximab dose was 1.5-fold higher in patients receiving a dose increase than in patients receiving an interval reduction (after recalculation to 8-weekly intervals). Costs are estimated after dose increase on 3506 euro plus 316 euro (cost price for one administration in day care clinic) per 8 weeks in an average 70 kg patient (Dutch tariff 2003 686 euro per 100 mg infliximab). After the interval reduction, infliximab costs are 2305 euro plus 462 euro for 1.5 administrations per 8 weeks. Furthermore, the observed efficacy was more pronounced in patients receiving an interval reduction, compared with patients receiving a dose increase. Although patient numbers are small, these findings are considered remarkable in the light of the high costs of infliximab treatment.

However, the open-label setting of this study excludes a comparison between the treatment groups. Randomized clinical trials with larger patient numbers are needed to confirm the observed differences in moderate responders receiving dose increase or interval reduction. Such a trial should include a treatment group receiving the standard treatment without treatment adjustments, as delayed responses and regression to the mean of disease activity might occur.

The results of this study show that RA patients with an initial moderate response on infliximab later on show different patterns of disease activity, i.e. further improvement, no change or a temporary response. Treatment adjustments show efficacy in all moderate responders, whereas non-responders often continue to have high disease activity despite treatment adjustments. The observed response was more pronounced in patients who received an interval reduction.

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CHAPTER 5

Dermatological conditions during TNFα blocking therapy in patients with rheumatoid arthritis: a prospective study

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Summary

Introduction | Various dermatological conditions have been reported during tumour necrosis factor alpha (TNFα) blocking therapy, but until now no prospective studies have been focused on this aspect. The present study was set up to investigate the number and nature of clinically important dermatological conditions during TNFα blocking therapy in patients with rheumatoid arthritis (RA).

Methods | RA patients starting on TNFα blocking therapy were prospectively followed up. The numbers and natures of dermatological events giving rise to a dermatological consultation were recorded. The patients with a dermatological event were compared with a group of prospectively followed up RA control patients, naive to TNFα blocking therapy and matched for follow-up period.

Results | 289 RA patients started TNFα blocking therapy. 128 dermatological events were recorded in 72 patients (25%) during 911 patient-years of follow-up. TNFα blocking therapy was stopped in 19 (26%) of these 72 patients because of the dermatological event. More of the RA patients given TNFα blocking therapy (25%) than of the anti-TNFα-naive patients (13%) visited a dermatologist during follow-up ($P < 0.0005$).
Events were recorded more often during active treatment (0.16 events per patient-year) than during the period of withdrawal of TNFα blocking therapy (0.09 events per patient-year, $P < 0.0005$). The events recorded most frequently were skin infections (n = 33), eczema (n = 20), and drug-related eruptions (n =15). Other events with a possible relation to TNFα blocking therapy included vasculitis, psoriasis, drug-induced systemic lupus erythematosus, dermatomyositis, and a lymphomatoid-papulosis-like eruption.

Conclusion | This study is the first large prospective study focusing on dermatological conditions during TNFα blocking therapy. It shows that dermatological conditions are a significant and clinically important problem in RA patients receiving TNFα blocking therapy.

INTRODUCTION

The introduction of biological agents such as TNFα blocking agents has dramatically changed the therapeutic approach to rheumatic diseases in recent years. TNFα blocking therapy has had a remarkable effect on disease activity in an increasing number of rheumatic diseases, including rheumatoid arthritis (RA) [1-3], juvenile idiopathic arthritis [4], ankylosing spondylitis [5,6], and psoriatic arthritis [7]. At present, two monoclonal anti-TNFα antibodies (infliximab and adalimumab) and one soluble p75 TNFα receptor (etanercept) are being used in rheumatological practice.

Various skin conditions have been reported in clinical trials, including urticaria, rash, and stomatitis (during infliximab therapy) [8]; rash and injection-site reactions (during adalimumab therapy) [3,9]; and injection-site reactions (during etanercept therapy) [2].

However, clinical trials are not designed to provide information about the occurrence of rare adverse events associated with TNFα blocking therapy. More severe cutaneous reactions, such as erythema multiforme, discoid and subacute cutaneous lupus erythematosus, atopic dermatitis, necrotizing vasculitis, and bullous skin lesions, have been reported, mostly as singlecase observations [10-15].

Larger observational studies such as biological registries are needed to provide information on the nature and number of such dermatological adverse events during TNFα blocking therapy. The aim of this study was to investigate whether dermatological conditions after TNFα blocking therapy are a significant and clinically important problem in RA patients receiving TNFα blocking therapy.

MATERIALS AND METHODS

Study design

In a prospective cohort study, all consecutive patients with a diagnosis of RA according to the criteria of the American Rheumatism Association [16] who were starting on TNFα blocking therapy at the Department of Rheumatology at the Radboud University Nijmegen Medical Centre were followed as part of a Biological Registry [17]. Approval was obtained by the hospital's ethics committee.

Patients were required to meet the criteria set out in the Dutch guidelines for biological therapies: a moderate to high disease activity score (DAS) based on 28 joints (DAS28 ≥ 3.2), and failure or intolerability of at least two disease-modifying antirheumatic drugs (DMARDs), including methotrexate, in adequate dosage regimens. Besides therapy with registrated TNFα blocking agents – infliximab, etanercept, and adalimumab – some patients were treated in clinical trials with lenercept, a soluble p55 TNFα-receptor [18].

The number and nature of dermatological conditions that led patients in this cohort to consult a dermatologist during follow-up were investigated. The RA patients treated with TNA-α-blocking agents who experienced dermatological events were compared with a control group of patients who had RA but had never had TNFα blocking therapy. The control patients were selected from the Nijmegen inception

cohort, in which 500 RA patients have been followed since 1985 [19]. Each control was paired with a anti-TNFα-treated patient for duration and season of the follow-up period, within a 2-month window.

Variables

Data collected at the start of TNFα blocking therapy were age, sex, duration of disease, presence or absence of rheumatoid factor (measured by ELISA; considered positive if results showed >10 IU/ml), antinuclear antibody (tested for by immunofluorescence on Hep-2 cells), number of DMARDs previously used, and start date of TNFα blocking therapy. Baseline information obtained included erythrocyte sedimentation rate (ESR), 28-joint counts for swelling and tenderness, and general wellbeing as indicated on a visual analogue scale, and the disease activity score (DAS28) was calculated [20].

Variables about which information was collected during TNFα blocking therapy were the use of concomitant DMARDs and prednisolone, dose and interval changes of TNFα blocking agents and, if appropriate, date and reason for discontinuation. All patients who visited a dermatologist during follow-up were identified. Clinically important dermatological events were defined as any new manifestation or any exacerbation of pre-existing skin disease during follow-up. A standardized chart review form was used to record the following: start date of event, dermatological history, medication, morphological description, localization, histopathological and immunohistological information if available, working diagnosis, additional investigations, topical and systemic therapeutic actions, outcome of event, and any available information on rechallenge.

Drug-related eruptions were defined as skin reactions with a probable or definite relation to the use of TNFα blocking agents, based on a time relation with the administration of the agent, morphological pattern, and/or histological information. Drug-related eruptions were classified morphologically according to the criteria of Fitzpatrick and colleagues [21]. Events were also classified as major or minor, major events being any requiring hospitalization.

Patient-years of follow-up were calculated for total follow-up, time on active therapy, and time after discontinuation of therapy (time off therapy). The number of events per year of follow-up was calculated for each RA patient for total time of follow-up, time on active treatment, and time off treatment, if appropriate.

In the control group, the following baseline characteristics were collected: age, sex, disease duration, rheumatoid factor, antinuclear antibody, DAS28, the number of DMARDs previously used, and prednisolone use. All visits to a dermatologist during follow-up were identified. Events were not recorded in the control group.

Statistical analyses

The baseline characteristics of RA patients on TNFα blocking therapy were compared according to whether or not the patients experienced dermatological events. The chi-square test was applied for dichotomous variables and Student's t-test was used for continuous variables. Nonparametric tests were applied when appropriate. The Wilcoxon signed rank test was used to compare the number of events per patient-

year of follow-up in patients receiving and patients not receiving active TNFα blocking therapy.

Univariate and multivariate logistic regression analyses were performed to identify possible predictive factors for the occurrence of a dermatological visit (independent variable, dichotomous) in RA patients on TNFα blocking therapy. Dependent variables tested were sex, age at diagnosis, rheumatoid factor, antinuclear antibody, disease duration, DAS28 at baseline, prior number of DMARDs, use of prednisolone, and duration of follow-up. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated.

The number of patients who visited a dermatologist was compared between RA patients on TNFα blocking therapy and controls, using the chi-square test. P values and ORs were calculated.

All tests were two-sided, with $P < 0.05$ considered statistically significant. Statistical analyses were performed using SPSS statistical software (v 12.0.1, SPSS Inc, USA).

RESULTS

Patients

A total of 289 RA patients started TNFα blocking therapy between June 1994 and December 2003. Their baseline characteristics are shown in table 5.1.

The median follow-up time was 2.3 years (range 0.02 to 9.6). The total follow-up time was 911 patient-years, with 627 patient-years representing active therapy.

Table 5.1. Baseline characteristics of patients with rheumatoid arthritis (RA) studied

	Given TNFα blocking therapy		Controls[a]
	All patients	Patients with dermatological events	
	N=289	N=72	N=289
Male sex, n (%)	89 (31)	20 (28)	110 (38)
Age (yr) at diagnosis, mean (SD)	44.5 (14.7)	43.4 (12.7)	54.6 (14.1)**
RF positive, n (%)	249 (87)	68 (94)	205 (71)*
Disease duration (yr) at baseline, median (range)	9.2 (0.1-44.9)	10.3 (0.3-44.9)[$]	6.2 (0.0-12.6)**
DAS28 at baseline, mean (SD)	5.9 (1.1)	6.1 (1.1)	3.6 (1.4)**
ANA positive at baseline, n (%)[b]	112 (50)	33 (49)	118 (41)
Prior DMARDs, median (range)	4 (1-10)	5 (2-8)	1 (0-6)**
Prednisolone at baseline, n (%)	112 (39)	34 (47)	21 (7)**

[a]Not given TNFα blocking therapy. [b] ANA at start was present in respectively 261 and 67 patients on TNFα blocking therapy. *P < 0.001, **P <0.0001, compared with RA patients on TNFα blocking therapy; [$]P < 0.001 compared with RA patients on TNFα blocking therapy who experienced no dermatological events.

Table 5.2. Dermatological events in patients with rheumatoid arthritis (RA) given TNFα blocking therapy

	Events	Time to event in months		Events during treatment	Major events	Histology	DMARDs**	Prednisolone**	Permanent withdrawal of anti-TNFα#
	N (%)	median*	range	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
infections	33 (25.8)	9.1	1.1-61.1	24 (73)	0	5 (15)	20 (61)	21 (64)	4 (12)
eczema	20 (15.6)	7.1	0.2-49.9	16 (80)	1 (5)	4 20)	8 (40)	7 (35)	3 (15)
drug eruption	15 (11.7)	1.9	0.1-18.8	15 (100)	1 (7)	12 (80)	6 (40)	6 (40)	7 (47)
ulcers	9 (7.0)	13.6	0.3-52.5	3 (33)	1 (11)	2 (22)	7 (78)	4 (44)	1 (11)
skin tumour benign	7 (5.5)	12.9	2.0-18.1	7 (100)	0	2 (29)	5 (71)	4 (57)	0
skin tumour malignant	5 (3.9)	4.5	1.1-38.0	4 (80)	0	5 (100)	2 (40)	2 (40)	1 (20)
xerosis cutis	6 (4.7)	8.9	4.2-26.3	6 (100)	0	1 (16)	4 (67)	1 (17)	1 (17)
vasculitis	5 (3.9)	12.0	1.5-49.9	4 (80)	0	4 (80)	3 (60)	5 (100)	1 (20)
actinic keratosis	5 (3.9)	26.3	4.5-112.9	2 (40)	0	3 (60)	5 (100)	2 (40)	0
CVI/varices	4 (3.0)	24.0	1.7-33.6	3 (75)	0	0	3 (75)	2 (50)	0
psoriasis/psoriasiform	3 (2.3)	15.5	8.4-50.1	3 (100)	0	3 (100)	0	2 (67)	1 (33)
edema	3 (2.2)	8.2	4.0-39.6	2 (67)	0	1 (33)	1 (33)	1 (33)	0
stasis dermatitis	3 (2.2)	17.5	14.6-42.1	3 (100)	0	1 (33)	1 (33)	1 (33)	0
seborrhoic dermatitis	2 (1.5)	0.4, 19.8	-	2 (100)	0	0	0	0	0
other events	8 (6.0)	5.0	1.9-25.9	6 (75)	0	4 (50)	4 (50)	2 (25)	2 (25)
total	128 (100)	9.1	0.1-112.9	100 (78)	3 (2)	47 (37)	69 (54)	60 (47)	21 (16)

*median and range given for 3 cases or more, individual data given for 2 cases or less. ** Number of patients with concomitant DMARDs and prednisolone at the time of event. #Permanent discontinuation of TNFα blocking therapy due to the event. CVI = chronic venous insufficiency

Seventy of the 289 RA patients (24%) received more than one TNFα blocking agent and 8 (3%) received more than two agents. Infliximab was administered to 167 patients, adalimumab to 108, etanercept to 78, and lenercept to 31.

Dermatological events were recorded in 72 of the 289 RA patients (25%) receiving TNFα blocking therapy and in 37 (13%) of the control group (n = 289). The odds ratio (OR) of TNFα blocking therapy for a dermatological referral was 2.26 (95%CI 1.46 to 3.50, P < 0.0005). Dermatological history of patients on TNFα blocking therapy consisted of fifty-six instances of dermatological conditions recorded in 34 patients (47%) and included, among others, 10 drug reactions – while the patient was receiving gold (7), nonsteroidal anti-inflammatory drugs (2), or methotrexate (1) – 10 cases of eczema, 9 of mycosis, 3 of other infections, and 5 of chronic venous insufficiency.

Predictive factors

In univariate analyses, duration of follow-up (OR 1.27, 95%CI 1.14 to 1.41, P < 0.0005) and of disease (OR 1.03, 95%CI 1.003 to 1.07, P < 0.05) were statistically significant predictive factors for a dermatological event. In a multivariate model, only duration of follow-up was a statistically significant predictive factor (OR 1.30, 95%CI 1.12 to 1.52, P < 0.001).

Dermatological events

One hundred and twenty-eight dermatological events were recorded during follow-up in RA patients on TNFα blocking therapy (0.14 event per patient-year), as listed in table 5.2. The event per patient-year ratio was 0.16 during active treatment and 0.10 off treatment (P < 0.001). The number of events recorded during or after treatment was 56 for adalimumab (0.12 event per patient-year), 49 for infliximab (0.14 per patient-year), 16 for etanercept (0.13 per patient-year), and 13 for lenercept (0.07 per patient-year). TNFα blocking therapy was permanently withdrawn because of dermatological events 21 times in 19 patients.

Infections

Thirty-three infections were recorded in 27 patients, consisting of 20 fungal, 11 bacterial, and 2 viral infections (see table 5.3). Two patients had had a previous episode of dermatomycosis. None of the patients required hospitalization. One patient, who temporarily discontinued adalimumab monotherapy twice because of elective surgery, developed a bacterial superinfection of pre-existing eczema after every restart.

Eczema

Eczema was diagnosed 20 times in 19 patients and appeared in various morphological patterns. Most events were described as erythematosquamous (n = 8) or erythematous (n = 3) lesions or plaques, localized on hands and feet (n = 3), arms and legs (n = 5), face (n = 1), neck (n = 1), and buttocks (n = 1). A vesicular rash on hands and feet was described five times. A papular rash was described in three cases, with localization around the eyes, on the back, and once on the back and lower legs. Diagnoses comprised dyshidrotic (n = 5), contact (n = 4), nummular (n = 1), atopic (n = 1), papular (n = 1), and nonspecific eczema (n = 8). Two patients had a prior history of dyshidrotic eczema.

Table 5.3. Skin infections in RA patients given TNFα blocking therapy

	Events	Time to event		Drug*	Active	Rechallenge treatment**	Permanent withdrawal of anti-TNFα#	Biopsy	Cultured Species##
	n	median	range	n	n	n		n	
fungal infections	20	8.7	1.1-61.1						
dermatomycosis	9			A 3, I 4, E 2	7		0	1	*Tr. verrucosum* (1), *Tr. rubrum* (1)
onychomycosis	3			A 3	3		0	0	
combination	5			A 3, I 1, L 1	4		0	1	*Tr. rubrum* (3), *Tr. mentagrofytes* (1)
candidiasis	3			I 3	2		0	0	*Candida* spp. (2)
bacterial infections	11	9.5	1.4-52.5						
folliculitis	5			A 3, E 2	4	yes, negative	1	2	*St. aureus* (1)
erysipelas	3			E 2, I 1	3	yes, negative	2	1	
bacterial superinfection of eczema	2			A 1, I 1	1	yes, positive	1	0	
furuncle	1			I 1	0		0	0	
viral - herpes zoster	2	17.3, 40.9[$]		A 1, I 1	0		0	0	

*A=adalimumab, I=infliximab, E=etanercept, L=lenercept. **During active treatment with TNFα blocking therapy. #Permanent discontinuation of TNFα blocking therapy due to the event. ## *Tr. = Trychophyton, ssp.* = species, *St. = Staphylococcus*. [$]Individual value

Biopsies were performed in five events. Histology showed dermatitis and spongiosis in all cases, with high dermal perivascular infiltration in three. One biopsy also showed mild psoriasiform acanthosis and another showed additional keratinocyte necrosis.

Three patients stopped TNFα blocking therapy because of the dermatological event, after which the lesions resolved. Hospitalization was necessary for treatment of eczema in one patient. In another patient the eczematous lesions recurred after adalimumab therapy was restarted. Adalimumab was continued and topical steroids were applied with good effect. TNFα blocking therapy had already been stopped in 4 patients before the onset of eczema and was continued in 13 patients, of whom 7 had persisting or recurring lesions. Therapy consisted mostly of topical corticosteroids.

Drug-related eruptions

Drug-related eruptions occurred frequently during the first 5 months of TNFα blocking therapy and were caused by all four TNFα blocking agents (see table 5.4). In two cases, a generalized drug-related eruption followed subcutaneous injection of etanercept. In two cases, the eruption developed during infusion (patient numbers 8 and 11, table 5.4). In the other cases the time of onset ranged between 2 and 57 days after the most recent infusion.

Most drug-related eruptions consisted of a combination of morphological patterns, including exanthema, urticarial eruptions, lichenoid skin lesions, and purpura. In four patients, an eczematous drug-related eruption was seen. Classification as drug-related eruption was based on a time relation with administration of the TNFα blocking agent, the morphological pattern, and/or histological information. Two patients had experienced a previous drug-induced eruption (1 dermatitis in response to gold, 1 dermatitis after indomethacin). The histological findings were compatible with the diagnosis in all cases. Perivascular infiltrations – predominantly lymphocytic – epidermal exocytosis, and hyperorthokeratosis were described. Interface dermatitis was described in three instances. One biopsy revealed focal infiltrations with marked vascular and endothelial proliferation.

Seven patients stopped and 8 patients continued therapy; 6 of them had a positive rechallenge and recurring lesions. One major event was recorded: an RA patient was hospitalized for an extensive eczematous eruption with urticaria on arms and legs (figure 5.1, and Patient no. 6 in table 5.4). Treatment consisted mostly of topical application of corticosteroids and sometimes of systemic antihistamines.

Tumours and actinic keratosis

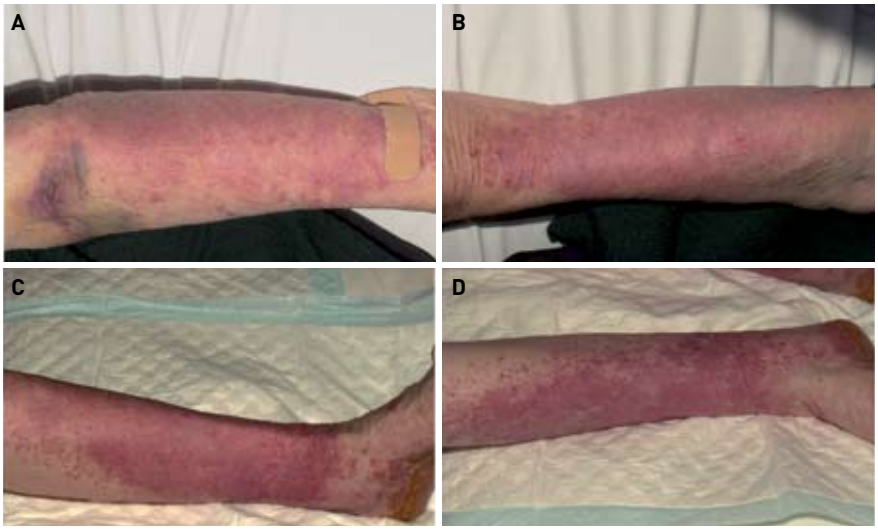
Events of skin malignancies were recorded five times, in four patients. One RA patient developed three basal cell carcinomas simultaneously on her left arm, right nostril, and right eyelid after 2.7 years of adalimumab therapy, which was subsequently stopped. One 74-year-old RA patient developed Bowen's disease on his right hand 2 years after adalimumab therapy had been stopped. The same patient later developed a squamous cell carcinoma on the left earlobe after the start of etanercept therapy. Other skin malignancies recorded were a squamous cell carcinoma (earlobe) after 1.5 months of adalimumab therapy and a low-grade basalioma (Pinkus epithelioma)

Table 5.4. Drug eruptions in RA patients

No	Age	Sex	Drug*	Route	Diagnosis	Clinical description	Localization	Time to event (m)	Biopsy	Comedication§	Therapy	Rechallenge	Permanent withdrawal anti-TNFα	Course
1	62	f	A	i.v.	eczematous eruption	erythematosquamous plaques and papules	neck/axillary/ legs	4,5	yes	naproxen	local	positive	No	recurring
2	71	m	A	i.v.	exanthematous lichenoid eruption	maculopapular exanthema	generalized	0,7	yes	prednisolone, naproxen, paracetamol	local	positive	Yes	recovery
3	77	m	E	s.c.	exanthematous eruption	macular exanthema	generalized	6,8	yes	prednisolone, naproxen, omeprazole	local	positive	No	recurring
4	67	m	E	s.c.	lichenoid eruption	macular exanthema, purpura	generalized	1,5	yes	diclophenac, omeprazole, triamterene, furosemide, candesartan	topical, systemic	no	Yes	recovery
5	69	f	I	i.v.	eczematous eruption	erythematous plaque	right cheek	0,1	yes	MTX, pantoprazole, atenolol, calcium, hydrochlorothiazide	topical	positive	No	recurring
6	88	f	I	i.v.	eczematous urticarial eruption	erythematosquamous macula, purpura	lower arms/ legs	3,9	yes	leflunomide, carbasalate, calcium, omeprazole, furosemide, simvastatin, paracetamol	topical	no	Yes	recovery
7	68	f	I	i.v.	eczematous urticarial eruption	erythematosquamous plaques, urticaria, excoriations, lichenification, purpura	generalized	10,3	no	AZA, furosemide, oxazepam, enalapril, spironolacton, metoprolol, flixotide, formoterol	topical, systemic	negative	No	recovery
8	60	f	I	i.v.	exanthematous eruption	stippled exanthema	generalized	0,5	yes	naproxen, omeprazole	topical	no	Yes	recovery
9	53	f	I	i.v.	exanthematous eruption	exanthema	upper arms/ legs	0,2	no	indometacin	topical	positive	No	recurring
10	73	f	I	i.v.	exanthematous eruption with purpura	exanthema, purpura	lower legs	18,8	no	MTX, folic acid, prednisolone, morfine, loperamide, lantanoprost	topical	no	Yes	recovery
11	70	f	I	i.v.	exanthematous urticarial eruption	exanthema, urticaria	arms/trunk	16,6	yes	leflunomide	no treatment	positive	No	recurring
12	35	f	I	i.v.	exanthematous urticarial eruption with purpura	macular exanthema, uricaria, purpura	trunk/axillary/ groins	1,9	yes	non	topical	-	Yes	recovery
13	58	f	I	i.v.	lichenoid eruption	Erythema, hyper-pigmentation, atrophy	upper legs	15,5	yes	leflunomide, meloxicam, metoclopramide, acenocoumarol, digoxin	no treatment	no	Yes	recovery
14	58	f	L	i.v.	exanthematous eruption	papular exanthema	generalized	0,4	yes	non	topical	positive	No	recurring
15	68	m	L	i.v.	exanthematous lichenoid eruption	maculopapular exanthema	generalized	1,7	yes	prednisolone, paracetamol	topical	negative	No	recovery

Events no.5 and 11 occurred in the same patient, as well as events no. 2, 3 and 15. *A=adalimumab, I=infliximab, E=etanercept, L=lenercept. §MTX = methotrexate, AZA = azathioprine.

Figure 5.1. Drug-related eczematous eruption



Eczematous drug-related eruption a patient with rheumatoid arthritis after infliximab therapy: Eczematous eruptions on the left arm (A) and right arm (B) and erythematous eruptions with purpura on the left leg (C) and right leg (D).

on the leg after 6 months of adalimumab therapy. In all cases, histology confirmed the diagnosis and therapy consisted of excision. No recurrences were seen.

Actinic keratosis was recorded in five patients (three receiving adalimumab, one infliximab, and one lenercept). Excision or cryotherapy was successful in four. One patient had recurring actinic lesions on the scalp.

Benign tumours were recorded seven times during TNFα blocking therapy. One patient experienced an increased growth of a facial telangiectatic nevus, present since childhood, 2 months after starting etanercept therapy. Seborrhoic keratosis (n = 3), oral hyperkeratosis (n = 1), histiocytoma (n = 1), and fibroma (n = 1) were also recorded.

Vasculitis

Vasculitis was recorded five times: four during and one after cessation of TNFα blocking therapy. The diagnosis was confirmed by biopsy in four cases. One patient developed a superficial necrotizing leukocytoclastic vasculitis with ulceration after 7 months of infliximab therapy, with complete recovery after discontinuation of infliximab. One patient developed a papular erythema in the groins after 5 years of adalimumab therapy. Histological examination was compatible with vasculitis with infiltration of mononuclear cells and presence of eosinophilic granulocytes. One patient developed a purpuric vasculitis on the legs after 1.5 months of lenercept therapy, improving spontaneously despite continuation of lenercept. One patient developed isolated digital vasculitis on his toes after one year of adalimumab therapy, which was continued. The lesions persisted. No biopsy was performed. One patient

Table 5.5. Other dermatological events

No	Age	Sex	Diagnosis	Drug*	Active treatment	Event	Clinical description	Localization	Time to event	Biopsy	Comedication#	Permanent withdrawal anti-TNFα	Therapy	Course
1	56,7	f	RA	A	yes	lymphomatoid papulosis-like eruption	macular erythematosquamous lesions	lower arms, upper legs and trunk	2,6	yes	naproxen	no	none	recovery
2	53,4	f	RA	A	yes	rosacea	diffuse erythema, scaling, teleangiectasias	head and face	1,9	yes	prednisolone, captopril, indometacin, midazolam	no	topical	persisting
3	74,5	f	RA	E	yes	pruritus	itch	trunk	2,5	no	none	no	topical	unknown
4	61,3	f	RA	I	no	ecchymoses	ecchymoses	hand and feet	25,9	no	AZA, prednisolone	no	topical	partial recovery
5	58,4	f	RA	I	yes	drug-induced SL	Discoid erythematous lesions, aphthous lesions, ANA positive, anti-ds-DNA positive	hands, face and scalp	20,0	no	MTX	yes	topical and systemic	recovery, no rechal-lenge
6	68,8	m	RA	I	yes	transient swelling of unknown cause	transient swelling 2x3 cm	scalp	20,0	no	MTX, folic acid, naproxen	no	none	recovery
7	52,9	f	RA	L	yes	dermatomyositis	livid erythema, raised CPK, decreased proximal muscular strength	inner upper arms and legs	2,5	yes	none	yes	none	recovery
8	53,4	m	RA	L	no	erythema nodosum	painful erythematous nodules	lower legs	7,4	yes	AZA, naproxen, paracetamol	no	topical	partial recovery

*A=adalimumab, I=infliximab, E=etanercept, L=lenercept. #MTX = methotrexate, AZA = azathioprine

developed a generalized urticarial exanthema after therapy with etanercept 2 years earlier. Current therapy consisted of hydroxychloroquine and prednisolone. Histology showed a mild leukocytoclastic vasculitis.

Ulcers

The nine events with ulcers included four pressure ulcers, two ulcers due to dependency edema, one traumatic ulcer, one ulcer secondary to an unguis incarnatus, and one ulcer without further specification. Biopsies were taken in two patients, but no signs of vasculitis were found. A patient had a pressure ulcer with secondary infection and a fistula on his ankle, which contained osteosynthetic material. The patient was admitted to the hospital for intravenous antibiotic therapy and infliximab was stopped for several months. After recovery, the patient restarted infliximab without recurrence of his skin problems. TNFα blocking therapy was continued in the other eight patients, and in four of these the ulcers recovered; follow-up was missing in the other four.

Stasis dermatitis, edema, varices and chronic venous insufficiency

In 10 patients, a dermatological consultation was recorded for stasis dermatitis (n = 3), edema (n = 3), varices (n = 2), or chronic venous insufficiency (n = 2). In one patient with extensive varices, infliximab therapy was stopped temporarily because of a complicating thrombophlebitis. One patient had edema of both legs of unknown cause, with livid discoloration and induration. One patient had lymphedema secondary to RA. All other events were considered to be related to comorbidity, other than RA.

Psoriasis and psoriasiform eruptions

Psoriatic or psoriasiform eruptions were recorded in three RA patients. One developed a vesiculopustular erythematosquamous rash on hands and feet after 9 months of adalimumab therapy. Histology showed a mixed psoriasiform and spongiotic dermatitis. A second RA patient developed psoriasis guttata-like eruptions on her lower legs after 4 years of therapy with adalimumab. The lesions diminished after adalimumab was withdrawn. A third patient developed a psoriasiform eruption on arms and legs after 16 months of adalimumab therapy. Histology obtained in the latter two patients was consistent with psoriasis.

Other dermatological conditions

Other dermatological conditions that occurred during or after TNFα blocking therapy included, among others, dermatomyositis (1), drug-induced systemic lupus erythematosus (1), and lymphomatoid papulosis-like eruption (1). Details are shown in table 5.5.

One RA patient developed a macular rash on the inner sides of the upper arms and legs after 2.5 months of lenercept monotherapy. A skin biopsy showed a nonspecific chronic dermatitis. A soft-tissue biopsy, including skin, fascia and muscle, showed fascial and muscular infiltration, consistent with dermatomyositis.

One RA patient developed a drug-induced systemic lupus erythematosus after 20 months of infliximab therapy in combination with methotrexate, consisting of discoid lupus erythematosus lesions on her hands and scalp, aphthous lesions, con-

version to antinuclear antibody positivity, and a positive anti-double stranded-DNA (titre 60 U/L). The skin lesions flared within one week after infusion and disappeared after discontinuation of infliximab.

A third RA patient developed macular erythematosquamous lesions on her lower arms, upper legs and trunk after 2.6 months of adalimumab monotherapy. Histology showed a dermal infiltration with CD30-positive atypical T cells. Although the lesions appeared to be lymphomatoid papulosis, they completely disappeared within 6 weeks. Adalimumab was not stopped. This patient developed a large-cell anaplastic non-Hodgkin lymphoma 2 years later.

DISCUSSION

The present study is the first large prospective study focusing on dermatological conditions in RA patients on TNFα blocking therapy. Of the patients studied, 25% needed a dermatological consultation, compared with 13% in a RA control group, naive to TNFα blocking therapy. The number of dermatological events per patient-year was significantly higher during treatment than after treatment with TNFα blocking therapy. Dermatological events led to withdrawal of TNFα blocking therapy in 19 patients of 72 patients (26%). The events recorded most frequently were skin infections, eczema, and drug-related eruptions. Some other interesting events were recorded, such as psoriasis, drug-induced systemic lupus erythematosus, dermatomyositis, and a lymphomatoid papulosis like eruption.

RA is known to be associated with dermatological conditions such as vasculitis, nodulosis, palmar erythema, and bullous pemphigoid, among others [22,23]. At present, information on the incidence and prevalence of dermatological conditions in RA mainly originates from cross-sectional or retrospective studies [24-26]. Few prospective studies have been conducted focusing on specific conditions affecting the skin [27,28].

In establishing a relation between the use of a drug and the occurrence of dermatological conditions, various factors must be considered. Information on clinical and histological patterns, time and dose relation, dechallenge and rechallenge, and analogy with previously reported cases can provide support in assessing the plausibility of such a relation [29]. The underlying disease and concomitant medication also need careful consideration, as they can provide alternative explanations.

In this study the largest group of dermatological events consisted of skin infections, mostly fungal infections and folliculitis. The use of TNFα blocking therapy has raised concerns regarding an increased susceptibility to infections, as TNFα plays an important role in host-defence mechanisms [30]. An increased incidence of tuberculosis has been described [31], as well as a growing number of serious infections with fungal, mycobacterial, and intracellular bacterial pathogens [32-34]. Infections of the skin have not been the subject of report in clinical trials and observational studies with TNFα blocking therapy. Cases of severe necrotizing fasciitis have been described [35,36].

Skin infections have been reported frequently in the normal population and especially in RA patients [24-26]. Host defence impairments resulting from the

underlying disease might play a role in an increased susceptibility to skin infections in RA patients, as well as the use of corticosteroids and DMARDs such as methotrexate [28,37], which were recorded frequently in the present study (see table 5.2). They could provide an alternative explanation for the occurrence of skin infections.

However, most infections occurred during active treatment with TNFα blocking therapy, a finding that could suggest at least a relative contribution to an increased vulnerability to skin infections in the study population. In one patient, a bacterial superinfection of eczema occurred twice immediately after restart of adalimumab, showing a clear time relation.

For the description of the recorded drug-related eruptions, a clinico-morphological classification was chosen [21]. Four eruptions with a time relation and clinically or histological distinct drug-induced patterns also showed an eczematous appearance, both clinically and histologically. This is an unusual presentation for a drug-induced eruption and warrants further investigation.

Two drug-related eruptions occurred during infusion with infliximab or adalimumab, whereas all the others occurred after infusion. This will most likely not reflect the true ratio between acute and delayed reactions involving the skin, since acute reactions with skin involvement occur in 4% of the infusions and are usually treated by the rheumatologist without dermatological consultation [38].

Eczema was reported frequently in this study, even with various dermatitis conditions, such as xerosis cutis, stasis eczema, and seborrhoic eczema, classified as separate entities. Previous studies have reported RA, in which Th1 (T helper cell type 1) immune responses dominate, to be negatively associated with Th2-cell-mediated atopic disorders, such as eczema [39-41], although a similar incidence of eczema in RA and non-RA patients has also been reported [42]. TNFα blocking therapy downregulates Th1 immune responses [43], which might induce a shift of the Th1/Th2 balance towards Th2-dominated immune responses and which might promote an increased susceptibility to atopic disorders, such as eczema.

Although the time between the initiation of TNFα blocking therapy and the onset of dermatological conditions varied, a probable relation was seen in various events. These included, besides drug-related eruptions, events of cutaneous vasculitis, drug-induced systemic lupus erythematosus, dermatomyositis, and a lymphomatoid papulosis-like eruption.

An association between the use of TNFα blocking therapy and the induction of systemic lupus erythematosus and discoid lupus erythematosus is strongly suggested by the number of cases that have been published [10,11,13,44-46]. One case of discoid lupus erythematosus has been described on both etanercept and infliximab in the same RA patient [47].

Analogy with previous reports is also present for cutaneous vasculitis [13,47-49], although it is a known extra-articular manifestation of RA [22,23]. In the first case described, a probable relation with infliximab was present, based on the time relation and positive dechallenge. The other cases described were considered possibly related (Results section, Vaculitis, cases 2 and 3) and unlikely (cases 4 and 5). Almost all reported ulcers were considered secondary to other causes, as described.

Dermatomyositis has been reported previously, although the patient affected in that case had a different presentation, with raised creatinine phosphokinase, muscle atrophy, mechanic's hands, and vasculitis [17].

Another interesting finding was the occurrence of psoriasiform eruptions in three patients on TNFα blocking therapy. This observation is particularly interesting, since etanercept has received and infliximab is close to receiving FDA approval for treatment of psoriasis, after remarkable efficacy results in clinical trials [7,50,51]. The occurrence of guttate psoriasis has been reported after initiation of etanercept therapy for psoriasis in a placebo-controlled trial [51]. Another case report described the occurrence of psoriasiform eruptions with histologically a lichenoid dermatitis pattern in a patient with Crohn's disease [52].

An exacerbation of psoriasis was also seen in a patient with psoriatic arthritis receiving infliximab therapy. An additional analysis showed that 28 patients with various non-RA rheumatic diseases, including 12 juvenile idiopathic arthritis, 6 psoriatic arthritis, and 3 ankylosing spondylitis, had been treated with TNFα blocking therapy in the study centre. Five patients (18%) had visited a dermatologist for a dermatological condition during or after TNFα blocking therapy. The events included a drug-related eruption, eczema, and a facial mycosis in three patients with juvenile idiopathic arthritis and a superficial spreading melanoma in a patient with ankylosing spondylitis. This indicates that the occurrence of dermatological events during TNFα blocking therapy is not restricted to RA patients.

In the present study the control patients were matched for startdate and duration of follow-up period in order to control for time-related effects. A statistically significant relation between the use of TNFα blocking therapy and the occurrence of dermatological visits was shown. The two groups studied differed for most baseline characteristics. These differences result from the indication for TNFα blocking agents, which were reserved for patients who fulfilled criteria for active disease and DMARD failure (see methods section; study design), had a longer disease duration, and whose disease was perhaps more refractory.

However, it is considered unlikely that these factors influenced the relation between the use of TNFα blocking therapy and dermatological visits. In a multivariate regression model, no baseline characteristic showed a predictive value for the occurrence of a dermatological event in RA patients on TNFα blocking therapy. Also, a statistically significantly higher number of dermatological events was recorded during active treatment with TNFα blocking therapy than after the therapy had been stopped.

CONCLUSION

This is the first prospective study showing a relation between TNFα blocking therapy and the occurrence of dermatological conditions. Future prospective studies are needed to investigate the incidence and the pathogenesis of the encountered events, because they are a clinically significant problem in RA patients receiving TNFα blocking therapy.

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CHAPTER 6

Psoriasis-like dermatitis during TNFα blocking therapy; a case series and literature review

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Summary

Tumour necrosis factor alpha (TNFα) blocking agents are used for the treatment of chronic inflammatory diseases, like psoriasis, rheumatoid arthritis (RA), Crohn's disease (CD) and psoriatic arthritis (PsA). Three TNFα blocking agents, adalimumab, infliximab and etanercept, have currently been registered for treatment of moderate to severe plaque psoriasis after showing promising results in clinical trials. Interestingly, several cases of new onset psoriasis have been reported in the post-marketing phase. This case series describes the de novo development of psoriasiform skin lesions in 5 RA patients using TNFα blocking agents. Furthermore we review the literature concerning 110 published cases of patients developing psoriasiform lesions after TNFα blocking therapy. Most cases developed plaque psoriasis or psoriasis pustulosa palmoplantaris. Histology was consistent with psoriasis in 42 of 49 cases (86%).

The substantial number of cases with temporal associations and the positive rechallenge in some cases represent strong evidence for a relationship between the use of TNFα blocking therapy and the development of psoriasiform skin disease. Furthermore, a class effect is suggested by recurrence of these lesions after switching to other TNFα blocking agents. Immediate withdrawal of TNFα blocking agents does not seem mandatory, but is associated with a higher improvement rate. Future studies are needed to gain insight in the pathogenic mechanisms having a role in TNFα blocking therapy induced psoriasis.

INTRODUCTION

Tumour necrosis factor alpha (TNFα) blocking agents have proven important new therapeutic options in chronic inflammatory diseases, like psoriasis, rheumatoid arthritis (RA), Crohn's disease (CD) and psoriatic arthritis (PsA), amongst others [1,2]. Currently three TNFα blocking agents (adalimumab and infliximab, both monoclonal antibodies, and etanercept, a soluble TNFα receptor) have been registered for treatment of moderate to severe plaque psoriasis, after showing promising results in clinical trials [3-5].

Interestingly, the occurrence of new onset psoriasiform lesions and (pustular) psoriasis after initiation of TNFα blocking agents in RA patients has recently been described in several case reports [6-32]. Exacerbation of psoriasis during clinical trials has also been reported [13,15].

We describe five cases of new onset psoriasis in a cohort of 492 prospectively followed patients with RA on TNFα blocking agents and review the literature on this intriguing and paradoxal subject, as TNFα blocking agents have shown to be effective in reducing moderate to severe plaque psoriasis [12].

METHODS

The patients described in this case series were part of a longitudinal observational cohort study with RA patients starting on TNFα blocking agents, currently including 492 patients [12]. Adverse events were collected every three months in a standardized fashion. Cases one to four were referred to a dermatologist for further evaluation. Case five was retrospectively reviewed by the authors.

For the literature review articles were collected systematically. The Pubmed medline database was searched using a query combining a search string for psoriasis (psoria* OR palmoplanta*) with a search string for TNFα blocking agents (tumor necrosis factor OR tumour necrosis factor OR infliximab OR adalimumab OR etanercept OR anti-tumour necrosis factor OR anti-tumor necrosis factor OR TNF OR anti-TNF). The results were limited to publications after 1993 and in English, and were further specified by narrowing the query to citations including the terms: (onset OR induc* OR trigger* OR occur* [ti] OR develop* [ti]). Abstracts of retrieved citations were explored for cases describing the development of psoriasis or psoriasiform skin disease during TNFα. Additionally the references of retrieved articles were searched for missed cases.

OBSERVATIONS

Case 1

A 68-year old female RA patient developed guttate psoriasis after 4 years of adalimumab therapy. She had a rheumatoid factor (RF) negative non-erosive RA since 22 years, secondary osteoporosis and hypertension. Personal and family history was negative for psoriasis. The patient was treated with adalimumab in a randomized clinical trial,

after treatment failure to various disease modifying anti-rheumatic drugs (DMARDs). Other medication included butazolidin, calcium, omeprazole and atenolol.

During a period with recurrent urinary tract infections, vaginal candidiasis and sinusitis she developed an erythematosquamous rash with papules and plaques on her legs, trunk and lower arms, with a larger plaque around her umbilicus (figure 6.1a). Histology from a skin biopsy of her lower leg was consistent with the diagnosis papular eczema. Adalimumab was restarted and the lesions improved after treatment with topical steroids.

One year later she developed an erythematosquamous rash on the anterior side of her lower legs (figure 6.1b). Histopathology of a biopsy from her legs showed epidermal confluent parakeratosis, spongiosis, and acanthosis. Moreover the epidermis was infiltrated with lymphocytes and multiple Munro abscesses were seen in the stratum corneum. The papillary dermis did show a perivascular mononuclear cell infiltrate and mild edema with vessel proliferation (figure 6.2a). The diagnosis guttate psoriasis was made.

Adalimumab was withdrawn and treatment with topical steroids and calcitriol was initiated. The lesions resolved over a period of 10 months and did not recur.

Case 2

A 63-year old male patient presented with a pustular psoriasis after 9 months of adalimumab therapy. The patient had a 14-year history of RF positive erosive RA. His medical history further included epilepsy. Personal and family history was negative for psoriasis. He was enrolled in a clinical trial with intravenous (i.v.) adalimumab therapy, after treatment failure to various DMARDs, and he received 1 milligram per kilogram (mg/kg) every two weeks. Other medication included low dose prednisolone, piroxicam and diphantoin.

The patient presented with a pustular erythematosquamous eruption on the palms and back of his hands and later on the plantar and lateral aspect of both feet. Histopathology of a biopsy showed confluent hyper and parakeratosis with micropustules of Kogoj and microabcesses of Munro, irregular acanthosis and clubbing of the tips of the dermal rete ridges (figure 6.2b). In addition, the dermal papillae were edematous and contained dilated, tortuous capillaries. Histopathology was consistent with pustular psoriasis. Nineteen months after starting adalimumab, he developed typical nail pitting lesions on his fingernails and toenails.

Adalimumab was continued, topical corticosteroids and tar ointments were initiated. The skin lesions slowly resolved over the following year. The nail lesions persisted. Two years later he experienced a flare of psoriasis, which again slowly resolved, despite continuation of adalimumab.

Case 3

A 56-year old female patient was seen with a psoriasiform eruption after 16 months of adalimumab therapy. The patient had a 18-year history of refractory RF positive erosive RA. Her medical history consisted further of diabetes mellitus, Sjögren's syndrome and congestive cardiomyopathy. Personal and family history was negative for psoriasis. Adalimumab intravenously had been initiated in combination with

oral prednisolone 10 mg daily (d), after treatment failure of 7 different DMARDs. Concomitant medication was captopril, metoprolol, furosemide and insulin. She received adalimumab intravenously in a high dose of 5 mg/kg/week with reduction to 3 mg/kg/week after one year because of a good response. During adalimumab treatment she had experienced recurrent sinusitis and oral candidiasis.

The patient developed itching erythematosquamous plaques and follicular bound papules on the medial aspects of her feet, spreading out to her legs, trunk, back and arms. Histology showed focal spotty hyperkeratosis and parakeratosis (figure 6.2c). No neutrofils were seen in the parakeratosis. Irregular acanthosis was seen of the epidermis. Histopathology was consistent with a psoriasiform dermatitis.

Adalimumab was stopped because of a coinciding granulocytopenia. The skin lesions resolved after initiation of topical corticosteroids and calcipotriol and did not recur.

Case 4

A 77-year-old male man with a 13-year history of a refractory RF negative non-erosive RA developed a guttate psoriasis- like eruption after start of infliximab therapy. His personal history was negative for psoriasis, but he had a positive family history (son).

Infliximab 3 mg/kg intravenously was added to low dose oral prednisolone after treatment failure to 7 different DMARDs. After the first infusion the patient developed sharply demarcated guttatiform erythematosquamous lesions on arms and legs and experienced itch now and then.

A biopsy from the patient's left upper leg showed spotty parakeratosis with Munro-like micro-abcesses (figure 6.2d). Moreover, irregular acanthosis was seen, and the papillary dermis did show proliferation of vessels and extravasation of erythrocytes. The basal epidermis did not show an increased number of cycling keratinocytes. The histopathology was consistent with a psoriasiform dermatitis.

Potent topical corticosteroids were started and infliximab was stopped after five infusions (30 weeks of treatment), after which the lesions improved. Etanercept was started. The skin lesions slowly resolved during etanercept without recurrences.

Case 5

A 61-year old male patient with a RF positive RA since 19 years developed guttatiform sharply demarcated erythematous lesions, consistent with guttate psoriasis, after the third infusion of infliximab. His personal history was negative for psoriasis but his son suffered from plaque psoriasis. Infliximab monotherapy 3 mg/kg was initiated after treatment failure to methotrexate and sulphasalazine. He responded well after the first infusion but had no response after the 2nd and 3rd infusion. After the third infusion (week 6) he developed the earlier described generalized eruption with sharply demarcated guttatiform lesions on his lower arms, legs and back. The clinical presentation was consistent with psoriasis. Between week 6 and 14 after initiation of infliximab the lesions slowly improved without therapy. Infliximab therapy was stopped because of ineffectiveness after the fourth infusion (week 14). No recurrence of the lesions was seen.

Figure 6.1. Erythematosquamous rashes (case 1)

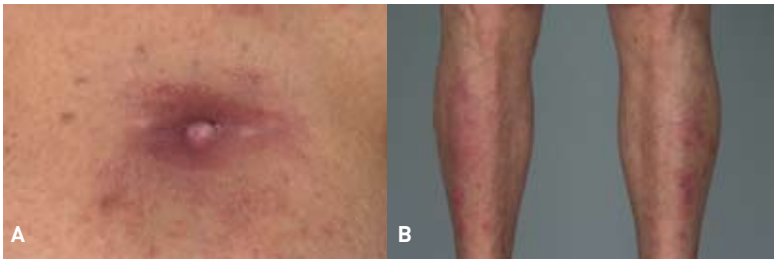
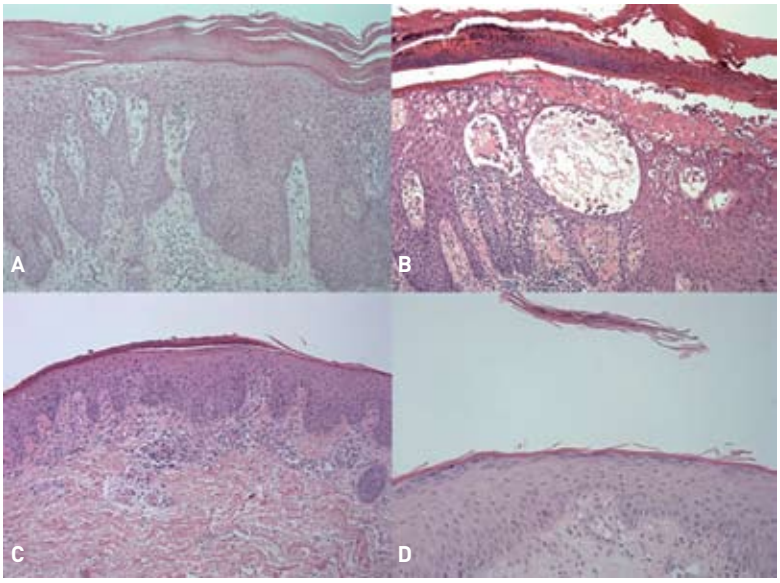


Figure 6.1A) The clinical image shows an erythematosquamous rash with papules and plaques on her legs, trunk and lower arms, with a larger plaque around her umbilicus (case one). Figure 6.1B) One year later she develops a non-papular erythematosquamous rash on the anterior side of her lower legs.

Figure 6.2. Histopathology figures



A) Histopathology shows a papillary dermis with a perivascular mononuclear cell infiltrateand mild edema with vessel proliferation. Histopathology is consistent with guttate psoriasis.
B) Histopathology of a biopsy shows confluent hyper and parakeratosis with micro-pustules of Kogoj and microabcesses Munro, irregular acanthosis and clubbing of the tips of the dermal rete ridges. This is consistent with psoriasiform dermatitis.
C) Histopathology shows focal spotty hyperkeratosis and parakeratosis. No neutrofils are seen in the parakeratosis. Irregular acanthosis is seen of the epidermis. Histopathology is consistent with psoriasiform dermatitis.
D) A biopsy from the patient's left upper leg shows the following histopathology: Spotty parakeratosis with Munro-like micro-abcesses. Moreover, irregular acanthosis is seen, and the papillary dermis shows proliferation of vessels and extravasation of erythrocytes. The basal epidermis does not show an increased number of cycling keratinocytes. Histopathology is consistent with psoriasiform dermatitis.

The five cases presented here belonged to a total group of 492 RA patients, treated with TNFα blocking agents in both clinical practice and clinical trials. All patients were ANA negative at the onset of psoriasiform skin eruptions and had no history of allergy or atopy. Initial responses to TNFα blocking agents were good in case 1 and 5, and moderate in case 2, 3 and 4. At onset of psoriasis disease activity was still low in case 1 (low inflammatory measures and no active arthritis) and moderate in case 2 to 5. No relationship was observed between the activity of psoriasis lesions and RA.

REVIEW OF CURRENT LITERATURE

We describe the development of psoriasis and psoriasiform skin disease in 5 RA patients treated with TNFα blocking agents. At present, a total of 115 cases of psoriasis or psoriasiform dermatitis occurring during TNFα blocking treatment in patients treated for other diseases than psoriasis, have been published, including the cases in this report. Furthermore, nine cases of exacerbation have been reported in patients with plaque-psoriasis, sometimes developing on new localisations or with different morphology [4,15].

CLINICAL PRESENTATION AND HISTOLOGY

Exacerbation of previous inactive psoriasis was reported in 6 patients with RA [13,14,24] and 3 patients with psoriatic arthritis [14,18,19], whereas all other cases described new onset psoriasis [6-8,10,11,13,14,16-36]. Both plaque-type psoriasis and palmoplantar pustulosis (PPP) represent the most frequently reported morphologies, sometimes occurring in combination (table 6.1). Other morphologies include guttate psoriasis, papular eruptions and non-palmoplantar pustulosis.

The majority of reported cases concerns patients with rheumatoid arthritis, followed by spondylarthropathies and Crohn's disease (table 6.2). Most patients with diseases, other than RA, had used infliximab, most likely reflecting the fact that adalimumab has only been recently marketed and etanercept is not effective in inflammatory bowel diseases. In patients with RA, all three agents were reported in near equal frequencies. Psoriasiform lesions typically occurred within the first year of TNFα blocking treatment (70%) with a reported median time to onset of 7 months (range 3 days - 62 months). No differences were seen between the three TNFα blocking agents. Family history was positive in 7 of 64 cases (11%). Smoking habits, which have been reported to be present in 95% of PPP patients at onset [37], were addressed in only four cases of PPP; three were positive.

The clinical presentation of anti-TNFα-induced psoriasis differs with respect to prevalence from the known psoriasis spectrum, as palmoplantar pustulosis and, to a lesser extend, scaling papular or guttatiform lesions were frequently described. Etanercept use was associated with a slighty lower number of PPP cases (8 of 24, 33%), compared to infliximab (32 of 72, 44%) or adalimumab (12 of 19, 63%). Furthermore, PPP was less frequently reported in Crohn's disease (2 of 14), than in rheumatoid

Table 6.1. Types of psoriasiform eruptions reported during TNF blocking therapy

Type of psoriasis	Total	TNF blocking agent			Time until onset (m)	Nail involvement	Histological confirmation	Rechallenge positive	Recurrence after switch TNF blocking agent
		INF	ETA	ADA					
	n	n	n	n	median (range)	n	n	n	n
PPP	36	24	6	6	7 (1-62)	1	12 of 12	1 of 4	2 of 3
PPP and plaque-type	13	5	2	6	10 (3-36)	1	5 of 6	-	4 of 6
PPP and guttate	3	3	-	-	14 (1-18)	-	1 of 1	-	1 of 1
Non-palmoplantar pustulosis and plaque-type	6	4	1	1	8 (4-18)	3	5 of 5	1 of 1	-
Plaque-type	39	23	12	4	8 (0.1-48)	4	13 of 17	3 of 4	2 of 2
Plaque-type and guttate	7	4	2	1	5 (0.1-42)	-	2 of 4	-	0 of 1
Guttate	4	3	-	1	11 (3-42)	-	1 of 1	-	-
Other*	7	6	1	-	2 (1.5-41)	-	3 of 3	1 of 1	1 of 2
Total	**115**	**72**	**24**	**19**	**7 (0.1-62)**	**9**	**42 of 49**	**6 of 10**	**10 of 15**

Legend: *papular 2, follicular 1, unspecified 4. Abbreviations: ADA; adalimumab, ETA; etanercept, INF; infliximab, PPP; pustulosis palmoplantaris.

arthritis (30 of 63) or spondylarthropahy (15 of 27). In 49 cases histology was present. Histology of 42 cases was consistent with psoriasis or psoriasis-like dermatitis. Other described histological patterns were lichenoid and/or spongiotic [18,22,23], mostly in plaque-type psoriasis (see table 6.1). Biopsies from case 1 and 4 in the current report showed a histological pattern that could be consistent with psoriasiform dermatitis, whereas case 2 and 3 showed histology consistent with pustular psoriasis.

ACTION AND OUTCOME

In the 115 reported cases TNFα blocking treatment was withdrawn in 45 patients, continued in 59 patients and unmentioned in eleven. Skin lesions improved in all but seven patients who discontinued TNFα blocking treatment. Thirty one patients permanently discontinued the use of TNFα blocking agents. Ten patients restarted after improvement, six patients experienced a positive re-challenge. In four patients the lesions did no recur. In four other patients the lesions persisted despite a temporary discontinuation.

Fifteen patients switched to another TNFα blocking agent. Ten of these patients experienced a recurrence of psoriasis after start of a new TNFα blocking agent. One RA patient experienced recurrences on two other TNFα blocking agents [13]. Recurrences occurred after switching between the two monoclonal antibodies infliximab and adalimumab, as well as after switching between monoclonal antibodies and the soluble receptor fusion protein etanercept, and vice versa. These cases strongly suggest an association between the use of TNFα blocking agents and the occurrence of psoriasiform lesions. They furthermore implicate a class effect of TNFα blocking agents for inducing psoriasiform lesions, rather than a drug specific effect.

In 59 patients who continued TNFα blocking treatment improvement was reported in 32 cases with complete resolution in twelve cases (in ten other cases outcome was not mentioned). Psoriasis treatments consisted mostly of topical steroids and occasionally topical calcitriol, ultraviolet B treatment or systemic steroids. The outcome in the reported cases suggests that treatment of anti-TNFα induced psoriasis does not always necessitate withdrawal of TNFα blocking agents.

All five cases described here presented with RA (according to the revised ACR criteria) [38] so the possibility of an RA-mimicking psoriatic arthritis can be withdrawn. Skin lesions all occurred after reduction of RA disease activity by TNFα blocking treatment. Furthermore, comedication that can induce psoriasis, like β-blockers and certain NSAIDs (tenoxicam) had been used for many years, making a causative relation with the development of psoriasis-like dermatitis lesions unlikely.

PATHOGENESIS

The pathogenesis of the development of psoriasiform lesions during TNFα blocking therapy still remains unclear. Given the diversity in clinical presentation as well as histopathology in the five cases presented here, as well as published literature, we

Table 6.2. Psoriasiform eruptions during TNF blocking therapy; division by underlying disease

Underlying disease	No of cases	New onset	Time until onset (m)	TNF blocking agent			Age at onset (y)	Male gender	Histology consistent
	n (%)	n (%)	median (range)	INF n	ETA n	ADA n	median (range)	n (%)	n (%)
Rheumatoid arthritis	63 (55)	53 of 59 (90)	8 (0.1-62)	27	18	18	55 (29-78)	14 (22)	23 of 27 (85)
Spondylarthropathy*	27 (23)	23 of 26 (88)	8 (2-42)	24	3	-	44 (19-68)	16 (59)	6 of 7 (86)
Crohn's disease	14 (12)	14 of 14 (100)	6 (0.5-31)	14	-	-	31 (19-56)	5 (36)	9 of 10 (90)
Ulcerative colitis	3 (3)	3 of 3 (100)	10 (6-18)	3	-	-	36 (35-10)	2 (67)	2 of 3 (67)
Behcet's disease	3 (3)	3 of 3 (100)	6 (1.5-7)	3	-	-	49 (43-60)	3 (100)	1 of 1 (100)
Juvenile idiopathic arthritis	2 (2)	2 of 2 (100)	24**	-	2	-	13 and 16	2 (67)	-
Seronegative arthritis	1 (1)	1 of 1 (100)	12	-	1	-	51	1 (100)	-
Panuveitis	1 (1)	1 of 1 (100)	1.5	1	-	-	55	0 (0)	1 of 1 (100)
Disease unspecified	1 (1)	n.m.	6	-	-	1	39	1 (100)	-
Total	**115**	**100 of 109 (92)**	**7 (0.1-62)**	**72**	**24**	**19**	**48 (13-78)**	**42 (37)**	**42 of 49 (86)**

Legend: *ankylosing spondylitis 19, psoriatic arthritis 3, unspecified spondylarthropathy 1. **reported in one case only. Abbreviations: INF; infliximab, ETA; etanercept, ADA; adalimumab.

consider the possibility of a variety of different reaction mechanisms. Another possibility may be different presentations due to interindividual diversity of (HLA)-genetic make-up.

TNFα, a pro-inflammatory cytokine, plays a crucial role in the pathogenesis of inflammatory dermatoses such as psoriasis. This is illustrated by the fact that TNFα blocking agents are highly effective in reducing psoriatic lesions [3-5]. In addition, in lesional psoriatic skin increased levels of TNFα compared to controls have been found and correlated with the severity of the disease [39]. Moreover after successful treatment of psoriasis, TNFα levels in skin and serum reduce significantly [40].

Activated T-cells, keratinocytes, monocytes and dendritic cells in human skin produce TNFα. Key-players in the pathogenesis of psoriasis and target cells for TNFα are T-helper cells (CD4+), cytotoxic T-cells (CD8+), NK-T cells (CD3+ and CD94+ or CD161+), regulatory T-cells (CD4+ and CD25+), (mature) dendritic cells, endothelial cells and keratinocytes [41]. The immunological effects of TNFα include the expression of adhesion molecules, such as ICAM-1 and VCAM-1 and the production of vascular growth factors, facilitating the migration of activated T-cells into the epidermis [42,43]. Furthermore, TNFα is able to stimulate the production of other pro-inflammatory cytokines and chemokines also enhancing T-cell trafficking [44,45]. Although only one cytokine is targeted with TNFα blocking agents, its effect on the immunological network of the skin may be profound.

The overproduction of pro-inflammatory cytokines such as TNFα, or the lack of sufficient expression of anti-inflammatory cytokines may lead to chronic inflammatory dermatoses. In this respect Banchereau et al. formulated an interesting hypothesis regarding auto-immunity [46]. They stated that auto-immunity is driven by a dynamic system of opposing vectors (IFNα/IFNβ and TNF) stimulating the production of distinct types of dendritic cells. Overproduction of one type of cytokine/vector is able to induce auto-immunity. This hypothesis possibly holds true for psoriasis and drug induced psoriasiform lesions. Patients who develop psoriasiform lesions after starting TNFα blocking agents may counteract the action of the drug by overexpressing TNFα. This may explain the paradoxical reaction of the development of psoriasiform lesions after starting TNFα blocking therapy.

Another hypothesis concerns the role of bacterial infections in the pathogenesis of psoriasis. Bacterial infections of the upper respiratory tract may play a role in triggering guttate psoriasis [47,48]. In the presented cases two out of five patients presented with upper respiratory tract infections. In anti-TNFα clinical trials upper respiratory tract infections occurred frequently and tended to predominate in the anti-TNFα treatment groups [49]. Thus, anti-TNFα might increase susceptibility to upper respiratoty tract infections in patients, who possibly already possess a higher risk for developing infections, originating from the underlying disease, like RA, or the use of comedication, like methotrexate and prednisolone. This could result in an increased risk for developing psoriasis, in which the initial triggering processes, including antigen processing and T-cell activation, are not primarily driven by TNFα. Nevertheless the T-cell responses important in maintaining psoriasis inflammation are indeed driven by TNFα [50].

The role of fungal infections, which were also present in the reported 2 cases, in triggering psoriasis is less clear, as studies have been published with contradicting results [51,52].

CONCLUSION

Substantial number of cases with temporal associations and the positive rechallenge in some cases represent strong evidence for a relationship between the use of TNFα blocking therapy and the development of both plaque psoriasis and pustulosa palmoplantaris, as well as other psoriasiform skin disease. Furthermore, a class effect is suggested by recurrence with other TNFα blocking agents. Immediate withdrawal of TNFα blocking agents does not seem mandatory, but is associated with a higher improvement rate. Future studies are needed to strengthen the evidence for the relationship between psoriasis and TNFα blocking therapy, to gain insight in the pathogenic mechanisms having a role in TNFα blocking therapy induced psoriasis and to identify which patients on TNFα blocking therapy are at risk for development of psoriasis.

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CHAPTER 7

General discussion

OBJECTIVE

The objective of this thesis was to study the drug survival, effectiveness and safety of TNFα blocking therapy in RA patients. In addition to this treatment modulations of infliximab therapy were investigated. The main findings of these studies and their implications for clinical practice and future research will be discussed in this chapter in the context of current scientific literature on TNFα blocking therapy.

MONITORING TNFα BLOCKING THERAPY

Large registries have been set up world-wide for monitoring long-term complications of TNFα blocking therapy [1]. They have been initialised after the recognition of various potential hazards associated with the use of TNFα blocking agents in the pre-clinical and early post-marketing stages. In addition to safety aspects, these longitudinal observational studies would also be able to provide information on long-term effectiveness of different treatment regimes in clinical practice.

In Europe, a proposal to establish these registries has been followed by several countries, amongst others, England, Sweden and Germany [2-4]. In the Netherlands a two-centre registry has been set up in Nijmegen to provide detailed monitoring on all RA patients starting TNFα blocking therapy, as described in **chapter one** and **chapter two**. This initiative has later been followed by a more extended multicentre registry, called the DREAM-registry (Dutch Rheumatoid Arthritis Monitoring Registry) [5].

Differences between registries, like patients' characteristics and national prescription criteria, have to be taken into account, when comparing data on effectiveness and safety of this registry (**chapter two**) with data derived from other biologic registries. Table 7.1 provides an overview of the most important differences between this registry and three important reference registries.

Several registries have included larger patient numbers, sometimes nationwide (England and Germany) [2-4]. To date, they have reported mostly on etanercept and infliximab, as adalimumab registration followed late 2003. Some features distinguish the present registry from the other registries:

1. The registry collected detailed information on patient' and disease characteristics, including, amongst others, three-monthly disease activity scores, biochemical and serological markers, and detailed information on concomitant medication.
2. Disease activity measurements were carried out by assessors who all had followed the same assessment training and regular standardisation trainings at the RUNMC [12].
3. Treatment assignment to TNFα blocking agents occurred in a successive order, as the choice was primarily based on availability of TNF agents (due to etanercept reimbursement problems in the Netherlands) instead of patient or doctor preferences. Such a sequential assignment reduces the risk for confounding by indication, as for most patients only one treatment option was available per time period.

Table 7.1. Overview of some referenced biologic registries

Registry (country)	Nijmegen Biologics Registry	BSRBR	SSATG[$]	RABBIT
	Netherlands	England	Sweden	Germany
National criteria for the use of TNF blocking agents				
Disease activity	>3.2	>5.1	no restriction	no restriction
DMARD failure	at least 2 DMARDs incl. MTX	at least 2 DMARDs incl. MTX	at least 2 DMARDs incl. MTX	at least 2 DMARDs incl. MTX
Other criteria		compliance with BSRBR registration	compliance with standardized monitoring	
Registry characteristics				
Start date	1997	2001	1999	2001
TNF naïve	yes	yes	yes	no
Participation	regional	nationwide	southern Sweden	nationwide
No. of centres involved	2	multiple	8	multiple
Monitoring visits	3-monthly	6-monthly	3-monthly during the 1st year, subseq. 6 m	
Disease activity measurements	DAS28	DAS28	DAS28	DAS28
Estimated compliance %	>99%	80%	90%	-
Patients' characteristics from recently reported studies for ETA/INF*				
Patient numbers	30/368	1267/1612	440/721	551/343
Age, y (mean)	52/56	55/56	55/55**	54/54
Female, %	74/74	78/78	75/82	78/71
DAS28 at baseline (mean)	6.1/5.8	6.7/6.7	5.6/5.8	6.1/6.0
Concomitant DMARDs, %	57/78	48/94	56/86	50/89
Concomitant MTX, %	33/50	28/86	41/69	34/66**
Concomitant steroids, %	57/27	50/49	?/?	?/?

*Data extracted from chapter 2 and from references [2-4,6-11]. **Calculated estimates.
[$]The STAGG is combined with the Stockholm registry (STURE) in the Anti-Rheumatic Therapy in Sweden registry (ARTIS), covering 95% of the Swedish population [2].

4. The registry has included a large patient group, receiving long-term adalimumab therapy. The patients started adalimumab from 1997 onwards in RCTs, but were subsequently being treated in a compassionate use program similar to daily clinical practice.

DRUG SURVIVAL

Drug survival is a composite tool investigating both the effectiveness and the safety of therapy, as well as other factors influencing adherence to treatment, such as availability of other therapeutic options and withdrawal for other reasons, like for instance, patient preferences and pregnancy.

The drug survival rates reported in **chapter two** are relatively low, compared to survival rates reported previously in clinical trials and other longitudinal observational studies. Reported survival rates in RCTs vary around 80% after one year of treatment [13-16]. However, results from RCTs do not always translate well into clinical practice. A recent observational study showed that more than two third of all RA patients treated with TNFα blocking agents in daily clinical practice would not have been eligible for one or more of the major clinical trials, who have led to approval of these drugs [11]. In other words, these patients would not have been accepted for these trials on the basis of the inclusion and exclusion criteria which were used. In this observational study treatment response rates of eligible patients correlated well to the response rates reported in RCTs, but the response rates in patients not eligible were significantly lower; these patients were less successful on TNFα blocking therapy. These 'ineligible' patients had lower baseline disease activity, lower functional status and more severe comorbidity.

In post-marketing observational studies, the reported survival rates after one year of treatment ranged from 65% to 95% [2,4,17-20]. Differences between these studies might be explained by differences in patients' characteristics, prescription criteria, comedication, and previous use or availability of TNFα blocking agents. One difference is the relatively low percentage of patients treated with infliximab in our cohort who used concomitant methotrexate (MTX) (50% versus (vs) 66-86% in other registries), which has been shown to be associated with a better drug survival (see below). Half of the remaining patients used concomitant DMARDs, other than MTX, and half did not use any concomitant DMARD.

When taking a closer look at the different reasons for discontinuation, infliximab is stopped relatively more often because of toxicity, whereas etanercept is stopped relatively more often because of ineffectiveness. This difference has also been observed in another study [20].

EFFECTIVENESS OF TNFα BLOCKING THERAPY

Approximately 70% of all patients with severe longstanding RA responded to TNFα blocking agents, with 20-30% achieving a EULAR good response and 10-20% achieving

remission (**chapter two**). These rates are comparable to results from other registries [8,18,21]. The same is true for changes in DAS28 [11,18,22,23]. Disease activity over time and response to therapy did not differ significantly between the three TNFα blocking agents. However, to accurately study equivalence in effectiveness randomized head-to-head studies are warranted. At present, no randomised studies comparing TNFα blocking agents with each other have been carried out.

IMMUNOGENICITY AND EFFECTIVENESS

For all three TNFα blocking agents higher response rates have been shown in combination with methotrexate [14,24,25]. In patients treated with infliximab, antibodies directed against infliximab can occur. These anti-infliximab antibodies have been reported in up to 44% of the patients within one year after start of therapy [26,27]. The presence of anti-infliximab antibodies is associated with neutralization and increased clearance of infliximab, lower serum through levels of infliximab and lower response rates [26-29]. Concomitant use of methotrexate may suppress the formation of anti-infliximab antibodies [25]. In patients with Crohn's disease a direct association has been shown between use of concomitant methotrexate and lower anti-infliximab antibody titres, associated with a longer duration of response and less infusion reactions [30]. So, concomitant MTX therapy may reduce the level of anti-infliximab antibodies, thereby reducing clearance rates and yielding higher serum infliximab concentrations, which correlate with treatment response in RA patients [27,31,32]. Increasing the infliximab dose is another option that may reduce the level of anti-infliximab antibodies, possibly by induction of immune tolerance [27,31].

Formation of antibodies to TNFα blocking agents has also been reported with etanercept and adalimumab, although at lower rates [13,33,34]. In a recent study anti-adalimumab antibodies appeared in 17% of adalimumab treated RA patients and were associated with a decline in clinical response [35]. Anti-etanercept antibodies have not been associated with a decline in response [34].

COMBINATION OF TNFα BLOCKING AGENTS WITH DMARDS, OTHER THAN MTX

As shown in table 7.1, in a significant subgroup of patients anti-TNFα is started either as monotherapy or in combination with DMARDs, other than methotrexate. The reason will most often be failure to or intolerability of methotrexate. In these patients leflunomide is an important alternative for combination with infliximab. In **chapter three** we show that administration of infliximab after or concomitantly with leflunomide is safe and effective in RA patients. These observations are in line with other reports, although two small studies reported an increase in adverse events [36-41].

The combination with other DMARDs like azathioprine and cyclosporine is currently less extensively explored [36]. Combining infliximab with DMARD other than methotrexate needs further evaluation, including determination of anti-infliximab antibody rates.

INFLIXIMAB DOSING SCHEDULES

At present, anti-infliximab antibody testing is not part of daily clinical practice in case of insufficient response. Treating physicians can choose between increasing the dose up to a maximum of 7.5 mg/kg/8 weeks or reducing the interval to a minimum of 4 weeks. Pharmacokinetic modelling of infliximab RCT data showed that interval reduction might be more effective in raising serum concentrations [42]. In **chapter four** the effectiveness of both therapeutic options was shown in an open-label study where the choice for the adjustment was tailored by the observed disease activity pattern. The theoretical background for this strategy, as described in the chapter, followed from pharmacological and clinical observations [42-44]. However, for a direct comparison between interval reduction and dosage increase a randomised trial is warranted. Such a trial should include a treatment arm receiving no treatment adjustments, as in **chapter four** a delayed improvement response beyond 14 weeks was observed in some patients. Interestingly, the estimated cost of infliximab medication and day care showed a difference of approximately 1000 euro per 8 weeks per patient in favour of the interval reduction group.

SWITCHING OF TNFα BLOCKING AGENTS

In **chapter two** a substantial number of patients switched from TNFα blocking agent, mostly from infliximab to etanercept. The observed survival rates of second treatment courses were good and comparable to previous reports on switching of TNFα blocking agents [45,46].

In patients switching from infliximab to etanercept drug survival of etanercept was not influenced by the reason for discontinuation of infliximab. However, the group size is relatively small to draw any firm conclusions. A larger cohort study recently showed that reasons for discontinuation of a second TNFα blocking agent are related to the reasons for discontinuation of the first TNFα blocking agent [47]. A Spanish cohort study showed that drug survival rates were better when replacing the first TNFα blocking agent for adverse events [48]. Another retrospective study showed that etanercept maintained the same level of clinical benefit after stopping infliximab for adverse events [49].

Some studies have showed that survival rates of second TNFα blocking agents were decreased, although still at acceptable levels, compared to survival rates of first TNFα blocking agents [48,50]. These data are contradictory to a large cohort study showing a longer drug survival of the 2nd TNFα blocking agent compared to the 1st agent in RA patients switching for ineffectiveness, and comparable survival rates of the 1st and 2nd TNFα blocking agent in patients switching for adverse events [51].

In conclusion, switching between TNFα blocking agents can be effective, regardless of the reason for discontinuation. Conflicting results have been published regarding drug survival of the 2nd treatment, especially in patients switching for reasons of effectiveness. At present, there are no indications that one switching strategy is

preferable above another. Future research should include the identification of predictive factors, which might explain the observed differences in secondary drug survival.

SAFETY OF TNFα BLOCKING THERAPY

The inhibition of TNFα has an impact on cellular immunity and host defences against pathogenic micro-organisms. A number of disorders have been associated with the use of TNFα blocking therapy, as summarized in table 7.2. Further concern remains regarding possible associations to the occurrence of malignancies, especially lymphoma's. Although the incidence of lymphoma's in RA patients on TNFα blocking agents is increased, when compared to background incidence rates, the risk increment may result from the disease itself and the level of disease activity, which have been associated with an increased lymphoma risk [52,53].

Infections

TNFα blocking therapy may be associated with a significant increase in serious infections. Although a number of studies have reported similar infection rates between patient on TNFα blocking agents and controls [14,15,54,55], a meta-analysis of nine RCTs with infliximab and adalimumab demonstrated a higher rate of serious infections in RA patients on infliximab and adalimumab [56].

Reactivation of tuberculosis has been associated with the use of TNFα blocking agents [57-59]. To a lesser extend, opportunistic infections, like histoplasmosis, listeriosis, aspergillosis, coccidioidomycosis and candidiasis, and intracellular infections, like atypical mycobacteria and salmonella, are also seen more frequently during TNFα blocking therapy [60-62]. In a recent meta-analysis of nine RCTs approximately 10% of serious infections were attributable to opportunistic micro-organisms [56].

Three large observational studies also have shown an increased risk for serious infections in general with an emphasis on lower respiratory tract, skin/soft tissue infections and bone/joint infections [9,63,64]. Four percent serious intracellular bacterial infections were seen, including tuberculosis, listeria, legionella, atypical Mycobacteria and salmonella.

The observed rate of serious infections in our cohort of 4.6 per 100 pt-yrs (**chapter two**) is comparable to the estimated rates from clinical trials (1-6/100 pt-yrs) [15,24,42] and observational studies (5.3-6.4/100 pt-yrs) [9,63]. No other opportunistic or intracellular infections were observed, except for three tuberculosis reactivations and one salmonella enterica septic arthritis.

Skin conditions

Dermatological conditions are frequently observed during TNFα blocking therapy [33,65,66]. A broad variety of conditions, including skin infections, drug-induced eruptions, eczema, psoriasis and vasculitis, is reported in **chapter five**. An increased risk for skin infections during TNFα blocking therapy has been shown by other observational studies [63].

The event per patient-year ratio was higher during active treatment than after treatment withdrawal. As some patients had stopped because of dermatological events, a possible selection bias may have influenced these results. To eliminate this bias an additional analysis was performed excluding all patients who stopped TNFα blocking therapy because of dermatological events. The difference in events per patient-year decreased slightly, but remained statistically significant (0.14 vs 0.10, P<0.05).

Possible pathophysiological mechanisms in TNFα associated skin conditions may include hypersensitivity reactions, reduced barrier function, cytokine imbalances and T-helper cell type 2 predominance [chapter six and seven] [67-70]. During follow-up a number of psoriasiform eruptions were recorded, which are described in detail in **chapter six**. Substantial evidence has emerged, linking the used TNFα blocking agents

Table 7.2. Adverse events associated with TNFα blocking therapy

Adverse event	Reference
Infections	
- Serious infections: increased risk	[9,56,63,64,71]
- Tuberculosis reactivation	[57-59,72,73]
- Opportunistic micro-organisms: histoplasmosis, listeriosis, aspergillosis, coccidioidomycosis, candidiasis, cryptococcosis	[62,63,74-76]
- Other intracellular micro-organisms: atypical *mycobacteria, salmonella* species.	[60,62,76]
- Exacerbation of chronic *hepatitis B virus* infection	[77,78]
Immune mediated disorders	
- Hypersensitivity reactions; infusion and injection site reactions	Chapter 6 [16,79-82]
- drug-induced SLE	[83-87]
- demyelinating disease	[88,89]
Skin disease	
- vasculitis	Chapter 6 [70,90-95]
- eczema	Chapter 6 [66]
- psoriasiform eruptions	Chapter 7 [67,96-99]
- skin infections; bacterial (necrotizing fasciitis), viral (herpetic) and fungal	Chapter 6 [63,100,101]
Heart disease	
- progression of existing heart failure	[102]
- possibility of new onset heart failure	[103]
Haematological	
- aplastic anemia/pancytopenia	[104-106]

to new onset of psoriasiform reactions and exacerbations of pre-existing psoriasis [67,68]. New onset psoriasiform eruptions occur with all three TNFα blocking agents and in all diseases in which TNFα blocking agents are used. More than half of the reported cases describe palmoplantar pustular eruptions. Positive rechallenges after switching to another TNFα blocking agent suggest a class effect. The pathogenesis of this interesting and paradoxal reaction has not yet been resolved, although the inhibition of a TNFα regulated negative feedback mechanism of cytokine production by dermal plasmacytoid dendritic cells has been implicated [67].

PREDICTIVE FACTORS

Three studies in this thesis investigated the predictive value of patients' characteristics on outcome variables, all in stepwise multivariate analyses. In **chapter two** predictive factors were identified for drug survival, disease activity over time and adverse events. In **chapter three** the predictive value of ANA status on disease activity over time and adverse events was studied. In **chapter five** the predictive value of baseline characteristics on the development of clinically important dermatological events was studied.

Predictive factors for drug survival

Drug survival was predicted in multivariate analysis by concomitant DMARD therapy, which is in accordance with reports from other biologic registries [4,10,22]. One of these studies further reported concomitant MTX to be superior to combinations with other DMARDs. In our cohort a slightly better survival was seen in patients on concomitant MTX, compared to other DMARDs, although not statistically significant (data not shown). Other reported predictors, as shown in table 7.3, are all indicators of disease severity. The predictive value of C-reactive protein (CRP) is controversial. A high CRP at baseline may, as an indicator of acute systemic inflammation, indicate a larger potential for improvement [10]. On the other hand, high baseline CRP levels have been shown to correlate inversely with serum infliximab concentrations and with response to therapy in RA patients treated with infliximab [32]. In **chapter two** a high disease activity before start of TNFα blocking therapy was associated with high disease activity during treatment. In multivariate analysis no association with drug survival was seen.

Predictive factors for effectiveness

Several predictive factors for disease activity over time were identified by multivariate analysis, after correction for treatment centre, TNFα blocking agent and duration of follow-up. Results were in accordance with other observational studies, as shown in table 7.4. Some remarks can be made.

The observation in chapter two that concomitant corticosteroid use at baseline predicts higher disease activity over time may implicate that corticosteroid use is associated with more severe disease. This finding may not applicable across other registries, because of differences in prescription behaviour between countries. In

some countries TNFα blocking agents are used more often in combination with corticosteroids, sometimes up to 95% [7].

In table 7.4 predictive factors for response to therapy, according to the EULAR response criteria [107], are shown.

Predictive factors for adverse events

In **chapter two** the predictive value of baseline characteristics was investigated for the occurrence of adverse events in general and for major adverse events, as well as for the most frequently reported events, namely infusion reactions, infections and dermatological conditions. An overview is presented in table 7.5.

Currently, only a few studies have investigated predictive factors for the occurrence of adverse events. Salliot et al reported concomitant steroids and the number of previous DMARDs to be univariately associated risk factors for infection, but in

Table 7.3. Baseline factors in observational studies predicting drug survival of TNFα blocking agents (in multivariate analysis)

Outcome	Predictive factors at baseline** [references]
Longer survival on drug	Concomitant MTX vs monotherapy [this thesis] [4,10,22], (trend: [4])
	Concomitant DMARDs vs monotherapy [20]
	Concomitant non-MTX DMARDs vs monotherapy [this thesis]
	Concomitant MTX vs other DMARDs [10]
	Early RA [this thesis]
	Low age [4,10]
	High CRP [10]
	High functional capacity [10]
	Less previously used DMARDs [4,10]
	RF negativity [4]
	No previous use of biologics [50]
Longer survival to adverse event*	Concomitant MTX vs monotherapy [this thesis] [10]
	Concomitant non-MTX DMARDs vs monotherapy [this thesis]
	Concomitant MTX vs non-MTX DMARDs [10]
Longer survival to ineffectiveness*	Concomitant MTX vs monotherapy [this thesis], INF# only [10]
	Concomitant non-MTX DMARDs vs monotherapy, INF# only [10]
	Low disease activity at week 14 or 22 [20]

*Drug survival to discontinuation because of adverse event respectively ineffectiveness.

**Unless stated otherwise. #INF = infliximab

multivariate analysis only previous joint surgery was associated with an increased infection risk in a retrospectively investigated cohort of patients with various rheumatic diseases on TNFα blocking therapy [108]. Another study suggested concomitant steroid use and older age to be risk factors for severe pyogenic infections in a cohort of 87 RA patients [109]. A more pronounced association between corticosteroids and serious infections was shown in a large prospective study of RA patients, aged 65 years or more, on TNFα blocking therapy or methotrexate [110].

In **chapter three** the clinical significance of anti nuclear antibodies as predictor for adverse events was investigated. Antinuclear antibodies (ANA) are common in RA patients. Half to three quarter of all RA patients will have positive ANA testing at some time-point in the course of the disease [111]. The numbers of ANA positive patients were in agreement with previous smaller studies: approximately 30-50% of the patients are ANA positive at start of therapy. 35-70% of the negative patients will

Table 7.4. Baseline factors in observational studies predicting EULAR-response and remission on TNFα blocking therapy (in multivariate analysis)

Outcome	Predictive factors [references]
Low disease activity over time	Male gender [this thesis]
	High age [this thesis]
	Less previously used DMARDs [this thesis]
	No concomitant corticosteroids [this thesis]
	Concomitant DMARDs [this thesis]
	Low baseline DAS28 [this thesis]
Higher EULAR-response rates	Eligibility to major clinical trials: all [11]
	Concomitant MTX vs monotherapy: ETA* [8,22], trend for INF* [22]
	Concomitant MTX vs other DMARDs: ETA [22], trend for INF [22]
	Concomitant NSAIDs: ETA and INF [8]
	High baseline functional status: ETA and INF [8]
	Absence of smoking: INF [8]
Higher EULAR-remission rates	Concomitant MTX vs monotherapy: ETA [8,22]
	Male sex: ETA and INF [8]
	Low baseline DAS28: all [21], ETA and INF [8]
	High baseline functional status: all [21], ETA and INF [8]
	Less previously used DMARDs: ETA and INF [8]
	Concomitant NSAIDs: ETA and INF [8]
	Low age at start: all [21]
	Absence of osteoporosis: all [21]

*ETA = etanercept, INF = infliximab

convert to ANA positivity during therapy, while 83-96% of the ANA positive patients will remain positive [39,112-115].

ANA positivity at start and conversion to ANA positivity after start of TNFα blocking therapy were not associated with the occurrence of adverse events. This is in agreement with previous reports [39,114], although a more recent study has identified ANA positivity at baseline as a risk factor for infusion reactions [116]. This risk was higher in patients without concomitant methotrexate. In chapter two ANA positivity at baseline did not predict the occurrence of infusion reactions in a multivariate model. Next to ANA, anti-infliximab antibodies have been associated with an increased risk for infusion reactions [30,106,117]. The incidence of anti-infliximab antibodies is higher among patients not receiving concomitant DMARDs [30,106,118].

Table 7.5. Baseline factors in observational studies predicting the occurrence of adverse events during TNFα blocking therapy (in multivariate analysis)

Adverse events	Predictive factor [references]
Any adverse event	Concomitant steroid use [this thesis] Higher body weight [this thesis]
Major events	Concomitant steroid use [this thesis] Higher age [this thesis]
Infections	Concomitant steroids [this thesis] [110] Concomitant DMARDs [this thesis] Previous joint surgery [108]
Allergic reactions	Female gender [this thesis] Higher no. of previously used DMARDs [this thesis] For INF: ANA positivity at baseline, Monotherapy or non-MTX combinations, low age at disease onset, long RA duration [116]
Dermatological conditions	Higher body weight [this thesis] Higher age [this thesis]

Summary of conclusions

- Drug survival and response rates of TNFα blocking agents in clinical practice are lower than the rates observed in clinical trials.
- Drug-survival and effectiveness of TNFα blocking agents are positively influenced by the use of concomitant DMARDs, including MTX.
- The use of concomitant MTX and corticosteroids in RA patients on TNFα blocking agents are associated with an increased risk for infection.
- The combination of infliximab with leflunomide is safe and efficacious in patients with RA.
- Anti-nuclear antibodies do not predict the effectiveness of infliximab therapy or occurrence of adverse events in RA patients
- Different patterns of disease activity can be observed in moderate responders to infliximab treatment; a constant moderate response, a flare of disease activity or a gradually improving response. Titrating infliximab dose and interval based on response patterns significantly reduces disease activity.
- Interval reduction of infliximab may have a better cost-effectiveness ratio than dosage increase in RA patients with a moderate response.
- Dermatological conditions are an important and clinically significant problem following TNFα blocking therapy.
- Psoriasiform eruptions are paradoxal adverse events associated with TNFα blocking therapy.

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CHAPTER 8
Summary

INTRODUCTION

Over the past two decades major advances have been made in unraveling the inflammatory process in rheumatoid arthritis (RA). A dominant role for TNFα has been implicated, which has led to the development of a new class of drugs: TNFα blocking agents. Currently three TNFα blocking agents have been approved for the treatment of RA: the soluble p75 TNFα receptor fusion protein Etanercept (Enbrel®), the chimeric monoclonal anti-TNFα antibody infliximab (Remicade®) and the human monoclonal anti-TNFα antibody adalimumab (Humira®).

These agents have shown remarkable efficacy and acceptable safety profiles in clinical trials. Long-term safety and effectiveness, however, needs further elucidation in post-marketing observational studies, because patients participating in clinical trials are model patients and are not representable for our patients in daily clinical practice. Furthermore, important safety issues have emerged from the use of TNFα blocking agents, which warrant long-term observation.

In two rheumatological centres in Nijmegen (Radboud University Nijmegen Medical Centre and St. Maartenskliniek Nijmegen) a longitudinal observational study was set up to monitor the long-term effects of TNFα blocking therapy. The purpose of this study was to investigate the clinical aspects of TNFα blocking therapy in patients with RA. These aspects include, amongst others, drug survival, effectiveness, toxicity and treatment modulation, which form the main subject of this thesis.

CHAPTER 2

Chapter two describes the long-term drug-survival, effectiveness and safety of etanercept, infliximab and adalimumab in patients with refractory RA. Adalimumab patients originated from clinical trials. The results show comparability in disease activity and response percentages during follow-up, however, drug survival rates differed between the agents. Overall responses over time were: moderate 41-49%, good 22-33%, remission 12-24%. Adalimumab showed a more favourable survival, possibly due to trial effects. Infliximab showed a less favourable drug survival course due to adverse events and etanercept showed a less favourable survival due to ineffectiveness, possibly resulting form the small number of patients treated with etanercept. Overall, observed drug survival rates were relatively low, as compared to rates reported previously in clinical trials and observational studies.

Patients who switched to a second TNFα blocking agent showed no decrease in drug survival of the second treatment course. The largest group consisted of patients switching from infliximab to etanercept. In this group the reasons for infliximab discontinuation did not influence etanercept survival. Adverse events were reported frequently throughout the follow-up period, but led to drug discontinuation in less than 15%. Etanercept treated patients reported less adverse events, although patient numbers were small.

Predictive factors were identified by multivariate analysis for drug survival (concomitant DMARDs, disease duration), disease activity (gender, age, baseline DAS28, DMARD history, concomitant DMARDs and corticosteroids) and adverse events (weight, age, gender, DMARD history, concomitant DMARDs and corticosteroids).

CHAPTER 3

Most clinical trials have investigated TNFα blocking agents either as monotherapy or in combination with methotrexate. Although infliximab has been proven efficacious as monotherapy, combining it with methotrexate has yielded better treatment responses. In patients who fail on methotrexate or do not tolerate it, the concomitant administration of leflunomide can be an important alternative, but this combination has not been studied in clinical trials.

In chapter three the combination of infliximab and leflunomide in 57 patients is studied prospectively and compared to infliximab in combination with other DMARDs in 105 patients. No statistical significant differences were observed between the groups regarding baseline characteristics, drug survival, disease activity, treatment response and adverse events, indicating that the administration of infliximab after or simultaneously with leflunomide is safe and effective in RA patients.

In a subanalysis the incidence of antinuclear antibodies (ANA) at start and seroconversion during TNFα blocking therapy was studied, together with the predictive value of ANA positivity on effectiveness and safety. In both groups an increase in ANA positive patients was seen. ANA positivity at start did not predict response to therapy or the occurrence of adverse events. Conversion to ANA positivity during therapy also did not predict the occurrence of adverse events.

CHAPTER 4

In chapter four the disease activity and response to infliximab was investigated in an open label study with 76 RA patients. The aim of the study was to investigate different patterns of response with a focus on patients with a moderate (suboptimal) response and to investigate methods of optimizing treatment response in these patients. In patients with a moderate response after 14 weeks the disease activity was closely observed during the next interval and was used to guide treatment adjustments. Three distinct disease courses were observed after week 14: a further improvement to good response, a temporary response and a stable disease activity course. The latter two groups received an interval reduction respectively dose increase. Both resulted in significant improvements in disease activity, however, with different mean infliximab dosages. In good responders at week 14 the response was often sustained over follow-up, whereas non-responders showed modest or no improvement despite dose adjustments.

CHAPTER 5

Various dermatological conditions have been reported during TNFα blocking therapy, but until now no prospective studies have been focused on this aspect. In chapter five a prospective study is described investigating the number and nature of clinically important dermatological conditions in RA patients receiving TNFα blocking therapy. One fourth of all patients on TNFα blocking therapy experienced one or more dermatological event, and in one fourth of these patients therapy was permanently discontinued.

When compared with a group of prospectively followed RA patients, serving as control patients naive to TNFα blocking therapy and matched for follow-up period, patients on TNFα blocking therapy were referred to a dermatologist twice as frequently.

The events recorded most frequently consisted of skin infections, eczema, and drug-related eruptions. Other reported events with a possible relation to TNFα blocking therapy included vasculitis, psoriasis, drug-induced systemic lupus erythematosus, dermatomyositis, and a lymphomatoid-papulosis-like eruption. This study is the first large prospective study describing the frequent occurrence of various dermatological conditions during TNFα blocking therapy.

CHAPTER 6

Psoriasis occurring during TNFα blocking therapy is a paradoxal and interesting phenomenon, as all three TNFα blocking agents are recently accepted as effective treatment options for moderate to severe plaque psoriasis. This chapter describes in detail the development of psoriasis and psoriasiform skin lesions in 5 RA patients during TNFα blocking therapy. These cases were added to the 110 already published cases in which temporal associations and positive rechallenges provide strong evidence for a causative relationship between the use of TNFα blocking therapy and the development of psoriasis and psoriasiform skin disease. Furthermore, recurrences on other TNFα blocking agents suggests a class effect. When observing the outcome of published cases withdrawal of TNFα blocking agents does not seem mandatory, but is associated with a higher improvement rate.

CHAPTER 9

Samenvatting

INTRODUCTIE

Reumatoïde artritis (RA, ook wel chronische gewrichtsreuma genoemd) is een vorm van reuma die voorkomt bij een half tot één procent van de wereldbevolking. RA is een chronische ziekte die gekenmerkt wordt door een ontsteking aan de gewrichten. Deze zijn gezwollen, stijf en pijnlijk. Op den duur kan schade optreden aan het kraakbeen en het bot van het gewricht. Hierdoor ontstaan vergroeiingen en standafwijkingen, waardoor de functie van de gewrichten permanent verloren kan gaan. De ziekte wordt gekenmerkt door een wisselend beloop met rustige en actieve fasen van ontsteking. Tussen mensen met RA bestaan grote verschillen in de activiteit en het beloop van de ziekte.

Het genezen van de ziekte is (nog) niet mogelijk. Met ontstekingsremmende medicijnen probeert men de ziekte te onderdrukken. Stap één in de behandeling bestaat uit de zogenaamde NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), zoals ibuprofen en naproxen. Deze verminderen de pijn en de stijfheid, maar remmen het ziekteproces niet. Stap twee bestaat uit het toevoegen van krachtigere ontstekingsremmers, zoals prednison en DMARDs (Disease Modifying AntiRheumatic Drugs, bijvoorbeeld methotrexaat). Het remmen van de ontsteking met behulp van bovengenoemde medicijnen lukt bij een aantal mensen met RA, maar niet bij iedereen. Daarom blijft er een zoektocht gaande naar nieuwe en betere medicijnen voor de behandeling van RA.

De oorzaak van RA is onbekend. Bij mensen met RA vallen afweercellen de eigen lichaamscellen aan. Het eiwit Tumour Necrosis Factor alfa (TNFα) speelt hierbij een belangrijke rol, zo heeft men ontdekt in de laatste twee decennia. TNFα functioneert als een 'boodschapper eiwit' tussen de afweercellen in het lichaam en stimuleert ontstekingsreacties. Bij mensen met RA is er een teveel aan TNFα in hun gewrichten.

De ontdekking van de rol van TNFα bij RA heeft geleid tot de ontwikkeling van een nieuwe groep geneesmiddelen: de TNFα blokkerende middelen. Momenteel zijn in Nederland drie TNFα blokkerende middelen goedgekeurd voor de behandeling van RA:

- Etanercept (merknaam Enbrel®), een oplosbare TNFα receptor fusie eiwit.
- Infliximab (merknaam Remicade®), een chimerisch (opgebouwd uit een deel muizeneiwit en een deel menselijk eiwit) antilichaam tegen TNFα.
- Adalimumab (merknaam Humira®), een humaan (volledig menselijk) antilichaam tegen TNFα.

Alle drie de middelen binden zich aan TNFα moleculen en maken de TNFα moleculen onschadelijk. Wetenschappelijk onderzoek heeft laten zien dat deze middelen een sterke remming geven van de ontsteking bij RA. De effectiviteit en veiligheid op lange termijn dienen echter nader te worden onderzocht, mede omdat een aantal patiënten ernstige bijwerkingen heeft gekregen na gebruik van deze middelen. Een voorbeeld daarvan is het reactiveren van tuberculose, waardoor patiënten die vroeger tuberculose hebben gehad deze infectie opnieuw kunnen krijgen.

Twee reumatologie afdelingen in Nijmegen (van het Universitair Medisch Centrum Sint Radboud en de Sint Maartenskliniek Nijmegen) hebben samen een studie opgezet om de lange termijn effecten van behandeling met TNFα blokkerende middelen

te onderzoeken. Het onderzoek richt zich op aspecten van de behandeling in de dagelijkse praktijk, zoals

- De geneesmiddeloverleving: hoe lang gebruiken patiënten met RA TNFα blokkerende middelen vóórdat ze daarmee stoppen, bijvoorbeeld wegens bijwerkingen of omdat het middel de ziekte activiteit te weinig onderdrukt?
- De effectiviteit: in welke mate verminderen deze medicijnen de ziekte activiteit? Dit wordt uitgedrukt door onder andere het aantal gezwollen en pijnlijke gewrichten.
- De behandelrespons: hoeveel patiënten ondervinden een effect van de behandeling?
- De bijwerkingen.
- Het optimaliseren van de doseringsschema's: leiden individuele aanpassingen tot een betere behandeling?

Deze aspecten vormen de hoofdonderwerpen van dit proefschrift.

HOOFDSTUK 2

Hoofdstuk 2 beschrijft de effectiviteit, veiligheid en geneesmiddeloverleving op de lange termijn van etanercept, infliximab en adalimumab bij patiënten met ernstige RA. De studie laat zien dat de drie middelen vergelijkbaar zijn wat betreft de vermindering van ziekte activiteit en het percentage patiënten dat een effect ondervond van de behandeling (behandelrespons). Gemiddeld hadden 65% tot 80% van de patiënten een vermindering van de ziekte activiteit en was bij 12% tot 20% de ziekte activiteit verdwenen.

Het tijdstip waarop patiënten gemiddeld stoppen met de behandeling (de geneesmiddeloverleving) verschilde tussen de drie geneesmiddelen. Oorzaken voor deze onderlinge verschillen kwamen mogelijk voort uit het feit dat de groepen zelf te verschillend waren: de groep met etanercept patiënten was erg klein en de adalimumab patiënten hadden mee gedaan aan een wetenschappelijk onderzoek en waren dus vooraf geselecteerd. De drie middelen werden relatief sneller gestopt in vergelijking met eerder uitgevoerd wetenschappelijk onderzoek met deze middelen.

De groep met RA patiënten die overstapten naar een tweede TNFα blokkerend middel gebruikten dit tweede middel gemiddeld net zo lang als het eerste middel gebruikt werd. De grootste groep bestond uit patiënten die van infliximab overstapten naar etanercept. De redenen voor het stoppen van infliximab hadden geen invloed op de geneesmiddeloverleving van etanercept.

Tijdens de behandeling met de drie TNFα blokkerende middelen traden frequent bijwerkingen op, zoals infecties, huidafwijkingen en allergische reacties. Slecht 15% van deze bijwerkingen leidden tot het permanent stoppen van de behandeling. Tijdens behandeling met etanercept werden minder bijwerkingen gerapporteerd, maar het aantal patiënten dat met etanercept behandeld werd was klein, waardoor de resultaten vertekend kunnen zijn.

Voorspellende factoren konden worden aangetoond voor geneesmiddeloverleving (het gelijktijdig gebruiken van DMARDs, de ziekteduur), ziekte activiteit (geslacht,

leeftijd, ziekte activiteit bij start, DMARD voorgeschiedenis, gelijktijdig gebruik van DMARDs en corticosteroïden) en bijwerkingen (gewicht, geslacht, leeftijd, DMARD voorgeschiedenis, gelijktijdig gebruik van DMARDs en corticosteroïden).

HOOFDSTUK 3

Van therapie met infliximab is bewezen dat deze effectief als monotherapie, dat wil zeggen zonder gelijktijdig gebruik van DMARDs. Wanneer infliximab echter gelijktijdig gebruikt wordt met methotrexaat (combinatie therapie), dan leidt dit tot een sterkere vermindering van de ziekte activiteit bij patiënten met RA. Daarom wordt geadviseerd infliximab altijd in combinatie met methotrexaat te gebruikten. Bij patiënten die geen effect ondervinden van methotrexaat of het middel niet kunnen verdragen kan de combinatie met een ander DMARD zoals leflunomide met infliximab een belangrijk alternatief vormen. De combinatie van infliximab met leflunomide is echter nog niet goed onderzocht.

In hoofdstuk 3 is de combinatie van infliximab met leflunomide bestudeerd bij 57 RA patiënten en vergeleken met 105 RA patiënten die infliximab gebruikten in combinatie met andere DMARDs. De twee groepen waren vergelijkbaar met betrekking tot de patiënt karakteristieken bij de start, de geneesmiddeloverleving, de effecten op ziekte activiteit, behandelrespons en de bijwerkingen. De resultaten laten zien dat de behandeling met infliximab samen met of aansluitend op behandeling met leflunomide veilig en effectief is bij patiënten met RA.

Tevens werd in deze studie gekeken naar de betekenis van het voorkomen van antinucleaire antilichamen (ANA) in het bloed van RA patiënten die infliximab gebruikten. Antinucleaire antilichamen zijn antilichamen die gericht zijn tegen bestanddelen van de celkern (nucleus). Zij kunnen incidenteel voorkomen bij gezonde personen, maar worden vaker gezien bij mensen met bepaalde vormen van reuma. Uit het onderzoek bleek dat het hebben van antinucleaire antilichamen bij therapie met infliximab geen relatie had met het optreden van bijwerkingen of met minder effect van infliximab behandeling.

HOOFDSTUK 4

In hoofdstuk 4 is de ziekte activiteit en behandelrespons op infliximab therapie onderzocht in een studie met 76 RA patiënten. Infliximab wordt via een infuus (via een plastic buisje in een ader in de arm) direct in de bloedbaan toegediend. Na een opstartfase van 6 weken met 3 infusen krijgen patiënten elke 8 weken een nieuw infuus. Een infuus duurt gemiddeld twee a drie uur.

Het doel van de studie in hoofdstuk 4 was om verschillende patronen in het beloop van de ziekte activiteit tussen twee giften infliximab te bestuderen en zo verschillende typen in de behandelrespons te identificeren.

Hierbij lag de nadruk op de patiënten met een matige behandelrespons. Bij de patiënten met een matige behandelrespons na 14 weken behandeling werd de ziekte

activiteit nauwkeurig gemeten tijdens het volgende 8-weekse interval. Deze metingen werden vervolgens gebruikt als leidraad voor aanpassing van de behandeling. Drie verschillende respons typen konden op deze manier van elkaar worden onderscheiden na 14 weken: verdere verbetering tot een goede respons, een matige stabiele behandelrespons, en een goede maar tijdelijke behandelrespons waarna sprake was van een terugval met opvlammen van de ziekte activiteit. De laatste twee respons typen werden gevolgd door een behandelaanpassing, te weten een ophoging van de dosis respectievelijk een inkorting van het interval tussen twee infusen met infliximab. Beide aanpassingen leidden tot een duidelijke verbetering in ziekte activiteit. De gemiddelde dosering van infliximab verschilde tussen de twee aanpassingen. Bij patiënten met initieel al een goede respons bleef deze meestal aanhouden gedurende de totale follow-up, terwijl mensen zonder initiële verbetering na de start van infliximab ook geen of slechts een minimale verbetering lieten zien na latere dosis ophoging.

HOOFDSTUK 5

Verschillende huidafwijkingen zijn beschreven gedurende het gebruik van TNFα blokkerende middelen, maar tot op heden zijn er geen prospectieve (toekomstgerichte) studies gepubliceerd die dit aspect belichten. Hoofdstuk 5 beschrijft een studie die de soort en het aantal huidafwijkingen bestudeert in RA patiënten die gevolgd worden tijdens hun behandeling met TNFα blokkerende middelen. Een vierde van alle patiënten ontwikkelde een of meer huidafwijkingen. In een vierde van deze groep werd het TNFα blokkerende middel permanent gestopt.

In vergelijking met patiënten, die geen TNFα blokkerende middel gebruikten of hadden gebruikt, werden patiënten met TNFα blokkerende middelen twee maal zo vaak naar een dermatoloog verwezen vanwege huidafwijkingen.

De huidafwijkingen die het meest voorkwamen waren huidinfecties, eczeem en geneesmiddelenreacties. Andere huidafwijkingen met een mogelijke relatie tot het gebruik van TNFα blokkerende middelen waren onder andere vasculitis, psoriasis, systemische lupus erythematosus en dermatomyositis. Deze studie is de eerste grote prospectieve studie die aantoont dat het optreden van huidafwijkingen tijdens behandeling met TNFα blokkerende middelen een klinisch belangrijk probleem zijn.

HOOFDSTUK 6

Alle drie de TNFα blokkerende middelen zijn ook effectief gebleken als behandeling van psoriasis en mogen sinds kort hiervoor worden toegepast door huidartsen. Het is echter zeer merkwaardig en interessant dat tijdens de behandeling met TNFα blokkerende middelen bij patiënten die geen psoriasis hebben, psoriasis en psoriasiforme (psoriasis-achtige) huidafwijkingen kunnen ontstaan.

Dit hoofdstuk beschrijft in detail de ontwikkeling van psoriasiforme huidafwijkingen bij 5 RA patiënten tijdens TNFα blokkerende behandeling. Deze patiënten

werden samengevoegd met 110 al gepubliceerde gevallen, waarbij zowel een relatie in de tijd als het heroptreden na herstart van de TNFα blokkerende behandeling een sterk bewijs leveren voor een oorzakelijke relatie tussen het gebruik van TNFα blokkerende middelen en het ontstaan van psoriasis en psoriasiforme huidafwijkingen. Bovendien kwamen de huidafwijkingen terug de na de overstap op een ander TNFα blokkerend middel. Het stoppen van de TNFα blokkerende behandeling lijkt niet direct niet noodzakelijk, maar leidt wel vaker tot volledig herstel.

LIST OF ABBREVIATIONS

95%CI = 95% confidence interval
ACR = American College of Rheumatology
ADA = adalimumab
AE = adverse event
ANA = antinuclear antibodies
ANOVA = analysis of variance
AS = Ankylosing spondylitis
AZA = azathioprine
BD = Beçhets disease
CD = Crohn's disease
CI = confidence interval
CU = Colitis ulcerosa
DAS28 = disease activity score including 28-joint counts
DCP = daily clinical practice
DMARD = disease modifying antirheumatic drug
ELISA = enzyme-linked immunosorbent assay
ETA = etanercept
GEE = Generalized Estimating Equations
HCQ = hydroxychloroquine
HR = Hazard ratio
i.v. = intravenously
ICAM-1 = Intercellular adhesion molecule-1
IFNα = Interferon α
IFNß = Interferon ß
INF = infliximab
JIA = juvenile idiopathic arthritis
LEF = leflunomide
MoAb = monoclonal antibody
MTX = methotrexate
n.s. = not significant
NSAID = Non-steroidal anti-inflammatory drug
OR = Odds ratio
PPP = palmoplantar pustulosis
PsA = Psoriatic arthritis
pt = patients
pt-yr = patient-year
RA = rheumatoid arthritis
RCT = randomized clinical trial
RF = rheumatoid factor
RUNMC = Radboud University Nijmegen Medical Centre
s.c. = subcutaneously
SASP = salazopyrin (sulphasalazine)
sd = standard deviation
SMN = Sint Maartenskliniek Nijmegen
SpA = Spondylarthropathy
ssp. = species
St. = Staphylococcus
Th1/Th2 = T helper cell type 1/type 2
TNFα = tumour necrosis factor alpha
VCAM-1 = Vascular adhesion molecule-1
vs = versus

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CURRICULUM VITAE

Marcel werd geboren op 18 december 1970 te Arnhem. Op zijn tweede verhuisde hij naar Nijmegen. Hij voltooide het atheneum op de Stedelijke Scholen Gemeenschap Nijmegen in 1989, waarna hij met de opleiding Geneeskunde begon aan het UMC Sint Radboud. Zijn opleiding liep vertraging op, onder andere door een parallel lopende volleybal carrière. Tussen 1994 en 1999 speelde hij eredivisie volleybal en in 1995 nam hij met het Nederland-C team deel aan Universiade in Japan. In 1999 liep hij een keuze stage sport geneeskunde op Papendal en deed wetenschappelijk onderzoek op de afdeling Fysiologie. Hiervoor ontving hij in 2000 de aanmoedigingsprijs van de faculteit Geneeskunde. In datzelfde jaar behaalde hij zijn artsexamen, waarna hij gedurende 10 maanden werkzaam was als AGNIO Interne geneeskunde in het UMC Sint Radboud. In maart 2001 begon hij op de afdeling Reumatologie als onderzoeker. Dit heeft geleid tot het proefschrift dat voor u ligt. In 2005 begon hij in het kader van de opleiding tot reumatoloog aan de vooropleiding interne geneeskunde in het Rijnstate ziekenhuis te Arnhem. In 2008 vervolgde hij zijn opleiding op de afdeling reumatologie in de Sint Maartenskliniek te Nijmegen. Hij woont samen met Simone en ze hebben een dochter, Lieve.

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