

Modern treatment strategies in rheumatoid arthritis

Impact on, and predictors of, disease activity and disease course

Merete Lund Hetland

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Official opponents: Marjatta Leirisalo-Repo & Tore K. Kvien

Correspondence: Merete Lund Hetland, Department of Rheumatology RM, Glostrup Hospital, Nordre Ringvej 57, 2600 Glostrup, Denmark

E-mail: merete.hetland@dadlnet.dk

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THE 7 ORIGINAL PAPERS ARE

- Hetland ML, Stengaard-Pedersen K, Junker P, Lottenburger T, Ellingsen T, Andersen LS, Hansen I, Skjødt H, Pedersen JK, Lauridsen UB, Svendsen A, Tarp U, Pødenphant J, Hansen G, Lindegaard H, de Carvalho A, Østergaard M, Hørslev-Petersen K; CIMESTRA Study Group. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. *Arthritis Rheum* 2006 May;54(5):1401-9.
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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory disease affecting approximately 1% of the population. It primarily affects the small joints in a symmetrical pattern with a potential for progressive joint destruction, and extra-articular and systemic manifestations may also be present. Historically, RA has been a debilitating disease with few, insufficient treatment modalities, resulting in heavily impaired physical function, work disability, joint destructions, increased morbidity and mortality (8-10). It remains one of the most important challenges to improve and optimize the medical treatment of RA. Modern treatment strate-

gies aim at reducing inflammation and halting erosive damage. The cornerstones include early treatment with use of methotrexate (MTX) in adequate dosages either in monotherapy or in combination with glucocorticoids, other disease-modifying drugs (DMARDs) or biological agents. The optimum treatment strategy for rheumatoid arthritis has not been established, and issues such as initial mono- versus combination therapy, the role of glucocorticoids and the indications for therapy with biological agents are still in dispute.

Randomized clinical trials (RCTs) and observational cohorts are complementary tools to gain medical evidence and improve clinical practice. RCTs provide important data regarding head-to-head comparisons of drugs and treatment strategies, which may help advance the treatment of RA. However, RCTs involve only selected patients for limited periods of follow-up, which may limit the generalizability and translation of the results to clinical practice. In contrast, national, observational registries or cohorts represent an important source of real-life clinical data, with the potential to investigate clinical practice over time as well as differences in efficacy and safety of various treatments. Weaknesses of the registries include lack of randomization and risk of biases.

Although newer treatments are effective in most patients at the group level, many patients remain partial responders or non-responders. The early identification of patients with inadequate response to therapy is important, but not easy. Search for predictive markers, whether clinical, biochemical or imaging-based may help the clinician and the patient in selecting the best treatment for the individual patient and thereby avoiding or reducing medication that is ineffective, costly and has potentially serious adverse effects.

The primary focus of the present thesis is modern medical treatment strategies and their impact on disease activity and disease course in patients with RA.

AIMS

The overall aims of this study were to evaluate the effects of modern treatment strategies on disease activity and disease course in patients with RA, and to identify predictors of response to therapy.

The treatment strategies involved included:

- (A): Aggressive conventional treatment aiming at inflammatory control in patients with recent onset RA
- (B): Treatment with TNF α blocker in patients with RA and an insufficient treatment response to conventional treatment.

(A) was investigated in a randomized placebo-controlled clinical trial (CIMESTRA), whereas (B) was investigated in an observational, nationwide, longitudinal cohort study (the DANBIO registry).

The overall aims involved the following specific aims:

1. To investigate short- and long-term (1, 2 and 5 years) clinical and radiographical outcomes after aggressive treatment with methotrexate, placebo-cyclosporine/ cyclosporine and intraarticular betamethasone in patients with early RA participating in the CIMESTRA study (paper 1, 2 and 3).
2. To identify which baseline factors that were predictive of radiographical progression after 2 and 5 years in the CIMESTRA study (paper 3 and 4).
3. To evaluate the registration of serious adverse events and adverse events in patients treated with etanercept or in-

fliximab during the first 2 years of post marketing clinical use based on DANBIO data (paper 5).

4. To investigate whether changes in prescription practice in patients with RA treated with adalimumab, etanercept and infliximab affected treatment response and adherence to therapy based on DANBIO data (paper 6).
5. To identify which baseline factors that were predictive of a good treatment response after 6 months in RA patients treated with adalimumab, etanercept and infliximab in clinical practice based on DANBIO data (paper 7).
6. To investigate and compare the treatment responses, remission rates and drug adherences in RA patients treated with adalimumab, etanercept and infliximab in clinical practice based on DANBIO data (paper 7).

BACKGROUND

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a severe, chronic disease with a prevalence of approximately 1% in the adult population. The etiology remains largely unknown despite extensive research. It affects women more than twice as often as men, and disease onset may occur at any age, but peaks in the fourth and fifth decade of life (11). It is associated with high morbidity, increased mortality and reduced quality of life (8-10;12). The main feature of the disease is chronic inflammation primarily located to the synovial joints that are affected in a polyarticular, symmetrical pattern, but extra-articular and systemic manifestations such as rheumatic nodules and fatigue may also be present. Swelling and tenderness of the joints lead to impaired physical functioning, and irreversible joint destructions result in further loss of function. Since the etiology of the disease remains largely unknown, the treatments aim at inflammatory control and halted joint destruction.

MONITORING DISEASE ACTIVITY AND DISEASE COURSE

Standardized outcome measures for use in clinical trials were developed during the 1980's. For clinical outcomes, 20% improvement according to the American College of Rheumatology criteria (ACR20), ACR50 and ACR70 treatment responses as well as the European League Against Rheumatism (EULAR) response criteria based on the Disease Activity Score in 28 joints (DAS28) became widely used and proved successful in clinical trials (13;14). They reflect the magnitude of change in disease activity (either relative or absolute). Remission criteria, e.g. ACR remission (15), DAS remission (14) or CDAI remission (16) were also developed, reflecting whether disease activity is suppressed below a certain threshold. For the assessment of functional status, the Stanford health assessment questionnaire (HAQ) score became widely used in RCTs (17). Together with visual analogue scales (VAS) for pain, fatigue and global impact, the HAQ constitutes the most widely used patient-reported outcome measure in RA. In the 1970's quantitative radiographic scoring systems were developed that became widely used in RCTs (18;19), later followed by other scoring systems (20;21).

It is recommended internationally that the doctor use e.g. the DAS28, HAQ and VAS scores to monitor disease course in the individual patient (22), but this is only rarely done on a routine basis outside RCTs. With improved treatment options, there is a

growing need for electronic- or paper-based systems that can aid the clinician in a routine-based evaluation of the disease activity in the individual patient (23;24).

TREATMENT OF RHEUMATOID ARTHRITIS

Conventional treatments (DMARDs)

Intramuscular gold was the dominating DMARD until the mid 1980's. In the following years, MTX became increasingly used, and gradually it became the first drug of choice in the treatment of RA (25). Later, data on combination therapy emerged, suggesting an improved clinical response, but the radiographic results were not convincing (26-28). MTX, sulphasalazine, hydroxychloroquine, cyclosporine and leflunomide constitute the most widely used DMARDs today. It is a heterogeneous group of drugs, which are administered orally (with the exception that MTX can also be given parenterally) with partly unknown mechanisms of action (29).

MTX is a folate antagonist. It is cytotoxic in high doses, but not in the doses used for the treatment of RA. The mechanism of action in low doses remains incompletely understood. It has both clinical and radiographic disease-modifying effects (25) and has proven to be well suited for treatment combinations with other DMARDs as well as with the biologic agents. Sulphasalazine has anti-inflammatory and antimicrobial effects and is suitable for mono- or combination therapy with e.g. hydroxychloroquine and MTX (26;27). Hydroxychloroquine in monotherapy has only a modest effect on RA. Its main role in the treatment of RA is in combination with MTX and/or sulphasalazine. Cyclosporine is mainly used in low-dose in combination with MTX and reduces radiographic progression (30;31). It acts via T lymphocytes, which are considered to be central in the pathogenesis of early RA (32). Concerns about renal side effects has limited its use, although with low-dose regimens, side effects are few (33). Leflunomide blocks pyrimidine synthesis. Its clinical and radiographic effects match those of MTX (34). It is used primarily as an alternative to MTX in selected patients.

DMARDs have a delayed onset of action, whereas glucocorticoids relieve signs and symptoms within days, appear to have some disease-modifying potential (35), and are often used as bridging therapy. Intraarticular administration of glucocorticoids may be used to obtain rapid control of disease with minimum toxicity (36).

New treatment modalities (biological agents)

The development of biological agents opened a new era in the treatment of RA. Biological agents are complex protein molecules, which are created by molecular technology. Each class of biological agents is directed towards a specific cytokine or cell surface molecule involved in the pathophysiologic pathways in RA. The first biological agents that were registered were tumour necrosis factor alpha (TNF α) inhibitors: etanercept (FDA approved 1998) and infliximab (1999), followed by adalimumab (2002). Infliximab is a chimeric monoclonal antibody, administered intravenously. Etanercept is a fusion protein consisting of two identical chains of the recombinanthuman TNF-receptor p75 monomer fused with the Fc domain of human IgG1, and adalimumab is a human monoclonal antibody against TNF α , the latter 2 drugs are both administered subcutaneously.

Other biological agents have been approved for the treatment of RA: Anakinra (a recombinant form of the IL1 recep-

tor antagonist (IL1-RA, administered subcutaneously (2001)); rituximab (a B-cell depleting agent (2006)); abatacept (a recombinant dimerized form of cytotoxic T-lymphocyte antigen 4 (CTLA4) that blocks T-cell co-stimulation, administered intravenously (2005+2008)), tocilizumab (a human monoclonal antibody against the IL-6 receptor administered intravenously (2009)); and two recent TNF α blockers, which are both administered subcutaneously: certolizumab pegol (a pegylated Fab fragment from a humanized monoclonal antibody (2009)); and golimumab (a human monoclonal antibody (2009)). In the present thesis, the focus of biological agents will be on the initial 3 TNF α blockers: adalimumab, etanercept and infliximab.

In Denmark, biological agents for the treatment of rheumatologic diseases can only be prescribed and handed out by hospital departments of rheumatology. The use of biological agents represents a major economic burden to the national health care systems. In Denmark, there is at present (December 2009, data from DANBIO) approximately 4.500 ongoing treatment series in rheumatology. The total expenditure in 2009 was more than 800 million DKK (\approx 107 million Euro), compared to 31 million DKK in 2001.

Treatment strategies in RA

The treatment strategy generally applied up to the mid-80's was the "pyramid approach" with a base of anti-inflammatory drugs (aspirin and non-steroidal anti-inflammatory drugs) that were prescribed along with a basic program of physical therapy, rest and education. DMARD therapy was not initiated until after several years, and generally not until after radiographic evidence of joint damage. The rationale for this strategy was the perception that RA was a benign disease, and that DMARDs were very toxic (37). Indeed, the DMARDs used often had little evidence for clinical and radiological efficacy, and sometimes also an unfavorable safety profile. The pyramid strategy resulted in poor disease control with high disease activity, work disability and progressive joint destructions and increased mortality (8-10). When this became evident, the focus of treatment shifted towards early and aggressive use of modern DMARDs, including combination therapy to reduce inflammation and halt erosive damage (38-41).

The cornerstones of modern treatment strategies include early treatment, use of methotrexate in adequate dosages either in monotherapy or in combination with glucocorticoids, other DMARDs or biological agents, and treatment regimes that aim at disease control. The optimum treatment strategy for RA has not yet been established, and issues such as initial mono- versus combination therapy, the role of glucocorticoids and the indication for use of biologics are still in dispute.

In Denmark, treatment with TNF α blockers is indicated in patients with RA, who have an insufficient response to the traditional DMARDs. RA patients, who are DMARD naïve, are primarily treated with conventional DMARD therapy, of which MTX is the most commonly used. In case of lack of response or insufficient response to MTX (preferably also given in combination with another DMARD) the patient candidates for treatment with a TNF α blocker.

RCTS AND OBSERVATIONAL STUDIES

RCTs have provided invaluable data to help advance the treatment of RA. However, they have significant limitations such as heavy selection of patients, narrow indications and limited duration. Observational studies, in contrast, may monitor treatment

effects and adverse events in daily clinical practice with “real-life” patients during long follow-up periods. The limitations of observational studies include lack of randomization and blinding as well as risk of various biases.

The studies based on the CIMESTRA and the DANBIO cohorts focused on different aspects of modern treatment strategy: CIMESTRA was a RCT that investigated an aggressive use of conventional DMARDs in early RA, and aimed at clinical synovitis suppression. DANBIO, in contrast, is a national registry with an observational, longitudinal design that allows studies on biological agents used in routine care.

The CIMESTRA study

The CIMESTRA study was an investigator-initiated RCT involving 5 departments across Denmark (Hvidovre, Gråsten, Århus, Odense, Herlev). It was the first Danish initiative to establish a multi-center research project on treatment strategy in early RA. A steering committee was appointed with representatives from all departments. In addition to the main treatment project, a number of spin-off projects was launched, e.g. (4;42-44).

The purpose of the RCT was to investigate whether an aggressive and intensive treatment with DMARDs right after disease onset could lead to disease control and suppression of disease activity. The treatment strategy was considered by the steering committee to be the most optimal treatment of early RA when the study was planned in 1997.

The DANBIO registry

Denmark had no routine-based registration of RA patients treated in routine care on a wider scale up to the year 2000, as was the case in most other countries. Inspired by other registries in Europe (45-49), the marketing of the first TNF α blockers, etanercept and infliximab, triggered the formation of a nationwide, voluntary registry of all adult rheumatologic patients receiving biological agents. The DANBIO registry quickly gained wide acceptance among Danish rheumatologists after it was initiated in October 2000, with coverage of close to 90% of eligible patients and participation of all departments of rheumatology in Denmark (5;50). DANBIO has been approved by the National Board of Health as a national quality registry since 2006, after which the reporting to the registry became mandatory.

PREDICTORS OF RADIOGRAPHIC PROGRESSION AND OF TREATMENT RESPONSE

RA is a disease with a highly variable course, and it is unlikely that “one treatment that fits all patients” will ever be developed. Some patients do well with little treatment, while others do badly even with the most intensive treatment available. Despite an aggressive strategy in the treatment of early RA, 25-50% of patients progress radiographically within 1 year of diagnosis (1;51). Positive rheumatoid factor (RF) of subclasses IgM and IgA, genetic disposition, severe disease activity and early development of radiographic erosions are risk factors for radiographic progression at group level, whereas the ability of these factors to predict the disease course in individual patients is rather poor. More recent studies have shown that anti-bodies against cyclic citrullinated peptide (anti-CCP) and magnetic resonance imaging (MRI) may predict subsequent radiographic progression (52;53). It is also important to try to identify the patients who are most likely to benefit from a certain treatment, since some have raised concerns that too many patients are treated with expensive and potentially harmful drugs without much benefit. Thus, 70% of

patients who are treated with TNF α blockers do not achieve a EULAR good response after 6 to 12 months (54). Poor functional status has in two earlier studies of TNF α blockers been associated with an impaired treatment response, whereas there is controversy about the significance of concomitant treatment with MTX (55;56).

Identification and development of biomarkers, genetic factors, algorithms, or imaging techniques that may assist the rheumatologist in identifying correctly the patients at risk for progressive disease or the patients that will not benefit from a certain treatment may help the clinician to optimize treatment in the individual patient.

PATIENTS AND METHODS

STUDY DESIGN

The investigations comprised 2 different study designs:

CIMESTRA

The CIMESTRA study was a randomised, double-blind, parallel-group, placebo-controlled, investigator-initiated trial including 160 consecutive patients with early RA. The patients were entered from October 1999 to October 2002 from five rheumatological centres in Denmark (11 to 64 patients per centre). The patients were randomized in blocks of 4 into two treatment arms (monotherapy (MTX plus placebo-cyclosporine)) and combination therapy group (MTX plus cyclosporine). The initial double-blinding was maintained throughout the study period of 5 years.

Patients were screened for their eligibility for the study (table 1). After inclusion, they were seen by two investigators at baseline and every fortnight for 8 weeks, thereafter every 4 weeks during the first 2 years of the study. One investigator, who performed the joint score and did the joint injections, was blinded to all other aspects of treatment; the other investigator was responsible for treatment adjustments and handling of side effects. From year 3, the patients were seen by one investigator according to the local guidelines (minimum 3 to 4 times per year) with annual study visit (year 3, 4 and 5).

All excluded patients were followed on intention-to-treat basis and encouraged to show up for the annual visits.

DANBIO

The DANBIO registry is an observational, longitudinal, nationwide database that monitors rheumatologic patients in routine care. The 2690 patients with RA in the present studies were entered into the registry from Oct 2000 to Dec 1st 2007 from 27 departments of rheumatology in Denmark (1 to 269 patients per department).

After screening of the patient for treatment eligibility according to local guidelines, the rheumatologist was encouraged to register the patient at baseline and 2-3 times annually thereafter and at treatment switches. Patients were entered when they started treatment with TNF α blocker for the first time and followed until withdrawal or longer.

PATIENT COHORTS

The CIMESTRA cohort

The list of in- and exclusion criteria is shown in table 1. In brief, patients were recruited who fulfilled the ACR criteria for RA, had

less than 6 months of disease duration, were DMARD naïve, had active disease (at least 2 swollen joints) and were aged 18-75 years.

Table 1. In- and exclusion criteria for the CIMESTRA study

<p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. Synovitis by clinical examination in at least 2 joints 2. Compliance with the ACR criteria (1987) for RA 3. Duration of no more than 6 months (from the first anamnestic non-traumatic synovitis of at least 6 weeks' duration) 4. Written informed consent <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. Age less than 18 years or more than 75 years 2. Lack of co-operability 3. Previous treatment with DMARD 4. Corticosteroid treatment during the preceding 4 weeks 5. Contra-indications for the treatments: <ul style="list-style-type: none"> • Previous or present malignant or pre-malignant disease • Poorly regulated hypertension (diastolic blood pressure >90 mmHg) • Impaired renal function • Immunodeficiency diseases, including HIV • Severe cardiac or pulmonary insufficiency (NYHA III-IV, dyspnoea at rest) • Severe general arteriosclerosis • Severe granulocytopenia (<3MIE/l) or thrombocytopenia (<100MIE/l) • Impaired liver function (liver enzymes more than twice the highest normal limit) • Alcohol consumption > 3 drinks a week • Poorly controlled epilepsy • Lack of contraception in fertile patients • Pregnancy and lactation • Psoriasis • Poorly regulated diabetes • Anticoagulant treatment • Known allergy to the medicine • Medicament interactions • Ongoing parvovirus B19 infection (IgM positive) • Hepatitis B or C infection • Other inflammatory rheumatic diseases
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All patients were in addition offered inclusion into a MRI sub-study (4). Informed consent, all required baseline variables and radiographs at 3 or 5 years were available in 130 and 110 patients, respectively, and they were included in the prediction models (specific aim 2).

The DANBIO cohorts

Included in the DANBIO studies were patients who had RA with an insufficient response to DMARD treatment. The decision to start treatment with a TNF α blocker was taken by the treating rheumatologist. The first national guidelines for treatment of RA patients with TNF α blockers, issued year 2000, are shown in table 2. In brief, patients with severe disease activity despite treatment with DMARDs, including combination treatment with MTX were candidates for treatment with TNF α blockers. The DANBIO steer-

ing committee has issued recommendations for biological treatment since 2006 (table 3).

Inclusion criteria

- ACR 1987 classification criteria for RA
- At least 2 DMARDs, incl. methotrexate should have been used during minimum 4 months each without sufficient clinical effect (i.e. persistent synovitis of at least 6 joints). In case of unacceptable adverse events to the DMARDs and in patients with poor prognosis, deviations from this criteria may arise. Usually, combination treatment e.g. methotrexate, sulphasalazine and hydroxychloroquine or methotrexate plus cyclosporine should have been attempted
- No contraindications for TNF-alpha inhibitors (see below)
- Co-operable patient

Exclusion criteria

- Infection including chronic viral infections. Negative serologic tests for hepatitis B and C should be present before treatment start. HIV test is performed only if HIV infection is suspected
- Vaccination with living vaccines during treatment
- Malignant lymphomas and other malignancies
- Pregnancy and breastfeeding (anti-conception must be used during treatment)
- Development of lupus-like symptoms. The presence of positive ANA and anti-DNA is not a contraindication for continued treatment, but in cases with lupus-like symptoms, treatment should be withdrawn

Table 2. National guidelines for treatment with TNF α blockers from year 2000 (according to the "Vejledende retningslinier for TNF-alfa hæmmende behandling ved reumatoid arthritis")

Table 3. Guidelines for treatment of RA with biological agents issued year 2006 by the DANBIO steering committee in the annual report

Patients, who despite optimal treatment with DMARD have

- Active disease (DAS28 >3.2)
or
- Progression of radiographic erosions
or
- Continuous need for prednisolone > 7.5 mg daily

Due to the observational design with continuous inclusion of patients, the number of patients increased over time (table 4). Data regarding specific aim 3 were collected during the first 2 years of post-marketing use of TNF α blockers in Denmark (1999-2002), at which time a total of 419 patients had been included in the registry. For the investigation of changes in prescription practice over time (specific aim 4), five cohorts were identified according to the calendar year of treatment initiation (calendar year: 2000/2001 (n=273), 2002 (n=187), 2003(n=331), 2004 (n=534), 2005 (n=488)) with a total of 1813 eligible patients in the registry by Dec 31st 2005. For the investigation of drug efficacy and ad-

herence to therapy, 2326 RA patients who had initiated the first TNF inhibitor by Dec 1st 2007 were included (specific aim 5-6).

Table 4. DANBIO cohorts

RA patients in DANBIO cohort	Specific aim 3 (Paper 5)	Specific aim 4 (Paper 6)	Specific aim 5-6 (Paper 7)
No of patients started treatment with first TNF α blocker	419*	1813	2326
Treatment			
Adalimumab	NA	27%	29%
Etanercept	13%	20%	22%
Infliximab	87%	52%	49%
Other biologics than TNF α blockers	NA	1%	NA
Cumulated no of treatment years			
Adalimumab	NA	820	1349
Etanercept	64	787	1161
Infliximab	279	1861	2286
Coverage	90%	91-92%	88%
Overlap of patients		354 patient from paper 5	282 patients from paper 5, 1507 patients from paper 6, 275 of those 1789 patients appear in all three papers

NA: Not applicable; *: 10% of patients had diagnoses other than RA.

MONITORING DISEASE ACTIVITY AND DISEASE COURSE

Measures of disease activity

In the present studies, disease activity was assessed by standard clinical and laboratory measures: joint evaluation of swollen and tender joints (28 joint count in DANBIO, 40 joint count in CIMESTRA), the Danish version of the HAQ, scored without correction for devices (17), VAS for patient's pain, patient's global and doctor's global, serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (the latter only in the CIMESTRA study).

Based on these parameters a composite measure for disease activity (DAS28 score) was calculated on four variables (including ESR in the CIMESTRA study and CRP in the DANBIO study). Remission was defined according to the ACR remission (only CIMESTRA), DAS28 remission, and CDAI remission (only DANBIO).

Measures of disease course

In this thesis, disease course was defined as treatment response as well as disease progression as judged by radiographic changes.

Treatment responses were assessed by ACR20, ACR50 and ACR70 treatment responses as well as EULAR good or moderate treatment response in the present studies. Functional status was assessed by the HAQ score.

In the CIMESTRA study, radiographic progression was assessed by X-rays of hands (posteroanterior and Nørgaard (57)

projections), wrists (posteroanterior and lateral) and forefeet (anteroposterior view) that were obtained at baseline, ½, 1, 2, 3, 4 and 5 years. Initially (in paper 1, at one year), the x-rays were scored blinded to treatment group and to chronology in order by a modification of the Larsen method (19;58). From year 2, the x-rays (baseline, 1, 2, 3, 4, and 5 year) were scored according to the Sharp-van-der Heijde scoring method (21) by an independent senior musculoskeletal radiologist, who was blinded to treatment group assignment but not to chronology of the images. In this thesis, only Sharp scores (Total Sharp score (TSS), Erosion Score (ES) and Joint Space Narrowing (JSN) are reported. The estimated yearly progression rate was calculated according to the duration of the disease and the baseline score for each patient (59).

In DANBIO, x-rays of hands and wrists (posteroanterior projections) and forefeet (anteroposterior view) should be taken at baseline and after 1 and 2 years, thereafter at treatment switches. The x-rays in DANBIO were evaluated in a separate study, which is not part of the present thesis (60;61).

OUTCOMES

The CIMESTRA study

In the analyses after 1 and 2 years, the primary end point was the fraction of patients who achieved an ACR20 response. Secondary end points included ACR remission, DAS28 remission, cumulated dose of betamethasone, ACR50 and ACR70 responses and radiographic progression. ACR remission must have been present both at the annual visit and the preceding visit to be acknowledged, and no betamethasone injections were allowed to have been given at any of the two visits. The primary radiographic end point was change in total Sharp-van der Heijde score (TSS) from baseline (62).

In the extension study from 3 to 5 years, the primary efficacy end point was radiographic progression (change in total Sharp-van der Heijde score (TSS)) at 5 years compared to baseline. Secondary end points included radiographic progression at 3 and 4 years, as well as clinical remission and functional disability at 3, 4, and 5 years. Sustained remission was defined as being in ACR remission at both 3, 4, and 5 years.

The DANBIO study

In specific aim 3, the outcomes reported were the frequencies and types of adverse events as well as risk factors during treatment. In specific aim 4, the trend in treatment response was investigated in cohorts of patients with RA, who started treatment with a TNF α blocker between 2000 and 2005. The treatment response after 1 year was assessed by DAS improvement, DAS remission, EULAR response, ACR20/50/70 responses, LUNDEX corrected responses (see statistical section), and adherence to therapy. In specific aim 5 and 6, the main outcomes were ACR70 response, EULAR good response, DAS28 remission, CDAI remission and adherence to therapy.

TREATMENT REGIMENS

The CIMESTRA study

The treatment strategy was to achieve an early and sustained synovitis suppression by aggressive use of i.a. glucocorticosteroids and DMARDs. At inclusion, the patients were randomized into one of two treatment arms (see figure 1 for a schematic presentation of the CIMESTRA trial profile).

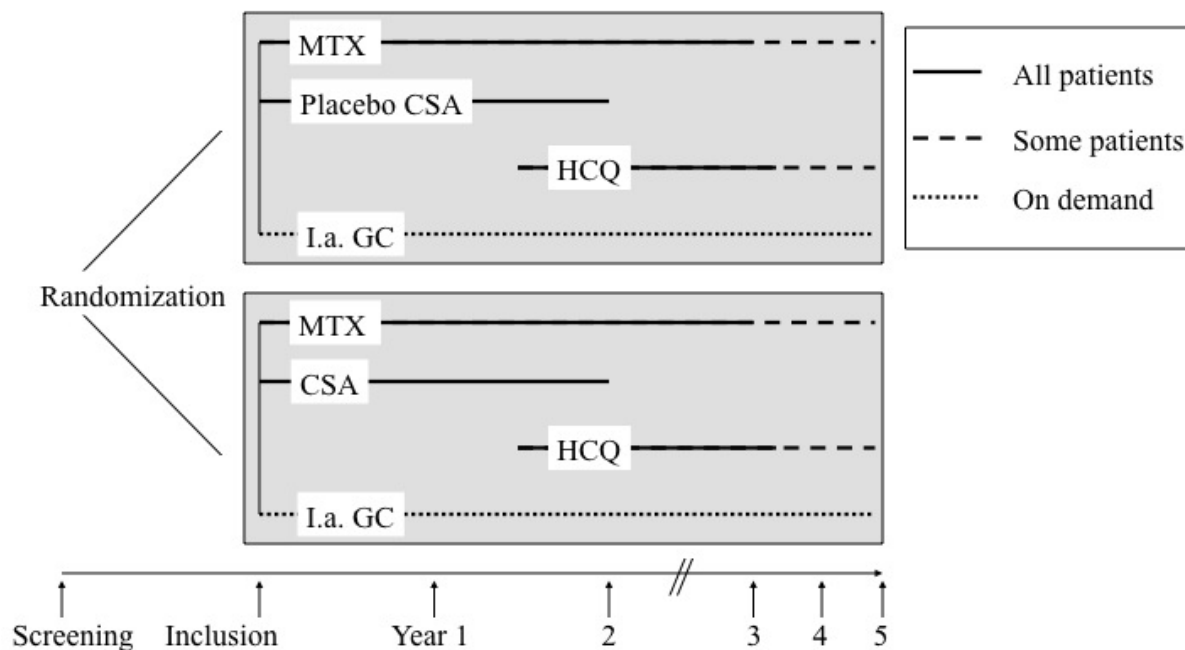


Figure 1. Schematic presentation of the Cimestra Trial Profile

In one arm, the patients were treated with MTX 7.5 mg weekly plus cyclosporine 2.5 mg/kg (combination group), in the other arm, the patients were treated with MTX 7.5 mg weekly plus placebo-cyclosporine (monotherapy group). At weeks 0, 2, 4, 6, 8, and thereafter every 4 weeks up to 52 weeks, the patients were given intra-articular betamethasone (7mg/ml) injections in all swollen joints (maximum 4 joints or 4 ml per visit). From week 8, if swollen joints were present, MTX dosage was increased by 2.5 mg/week every 4 weeks up to a maximum of 20 mg/week, and from week 28 a stepwise increase in cyclosporine/placebo-cyclosporine of 0.5 mg/day every 4 weeks to a maximum of 4 mg/kg. Joints were evaluated and injections were given by an independent, blinded, and trained assessor.

Cyclosporine/placebo-cyclosporine was tapered to zero by 0.5 mg/kg every 4 weeks from week 76, while MTX was continued. The long-term strategy was to withdraw MTX in patients who were in remission from year 3 and onwards. Hydroxychloroquine 200 mg/day was added in all patients at week 68, irrespective of disease activity. The principle of intra-articular injections of betamethasone in swollen joints and escalation of MTX dose was continued. Oral glucocorticoids were not allowed during the first 2 years.

In the extension of the trial from 2 to 5 years, the initial double-blinding was maintained. The frequency of visits was reduced from every 4 weeks to 3-4 times per year (according to local guidelines). The treatment strategy of strict clinical synovitis suppression by intra-articular glucocorticoids and conventional DMARDs was continued. Patients who did not achieve an ACR20 treatment response despite 20 mg MTX per week were switched to parenteral MTX for 3 months, followed by triple therapy (MTX,

sulphasalazine and hydroxychloroquine) for 3 months and after this excluded and switched to TNF α blocker treatment. Patients in ACR remission ≥ 12 months at 3, 4, or 5 years were offered gradual withdrawal from treatment (first MTX, then hydroxychloroquine).

During the first and second year, the dosage of cyclosporine/ placebo-cyclosporine was reduced if the serum creatinine level increased by more than 30% from baseline value. In the case of a persistent elevation, cyclosporine/ placebo-cyclosporine was withdrawn. Patients who developed hypertension ($>140/90$ mmHg) were treated with amlodipine, and the cyclosporine/ placebo-cyclosporine was reduced, or discontinued to resume normalisation of the blood pressure.

All patients received folic acid, and calcium and vitamin D supplementation. Patients with a Z score of < 0 in the femoral neck or lumbar spine measured by dual-energy x-ray scan at the start of the study received alendronate 10 mg daily. Mild analgesics were given on demand.

The DANBIO study

The treatment regimens reflected routine care. Prior to treatment initiation, patients were screened for tuberculosis, hepatitis etc. according to local and national guidelines (table 2). The TNF α blockers were prescribed in standard dosages unless the rheumatologist decided otherwise: Adalimumab 40 mg subcutaneously every fortnight. Etanercept was administered subcutaneously 25 mg twice weekly or 50 mg weekly. Infliximab was administered intravenously 3mg/kg at baseline, and after 2 and 6 weeks, thereafter every 8 weeks. Dose-escalation of infliximab either by reducing of intervals or increasing of dosage up to 10 mg/kg was allowed. For all three drugs it was recommended to treat in combination with MTX, although adalimumab and

etanercept could be administered as monotherapy. Choice of TNF blocker as well as concomitant treatment with other DMARDs or prednisolone was made according to the local guidelines. The rheumatologist recorded information on type of drug, start and stop dates (date of first missed dose) and reasons for withdrawal, and reported adverse events (AEs) in a standardized form at each medical visit. The questions included known AEs, for example: Any infection/eczema/allergic reaction or lupus-like symptoms since last visit? Regarding serious AEs (SAEs), death, life-threatening events, disablement, hospitalisation, and malignancy were registered. The rheumatologist judged whether a SAE was 'definitely', 'probably', 'possibly', or 'probably not' related to the treatment.

PREDICTORS OF TREATMENT RESPONSE

*The CIMESTR*A study

In addition to disease activity, conventional radiography, gender and age, the following potential baseline predictors of radiographic progression were assessed: Smoking habits, RF (IgG and IgM), anti-CCP, shared epitope (SE), serum CRP, ESR and MRI. Smoking habits were assessed by patient-reported questionnaire (ever/never smoker).

RF of IgM and IgA isotypes was detected by enzyme-linked immunosorbent assay (ELISA) as previously described with a few modifications (63). Cut-off levels were >16 IU/ml and >24 U/ml, respectively (~95th centile of healthy subjects). Anti-CCP IgG antibodies were determined by a second generation ELISA (Immunoscan RA kit, Euro-Diagnostica AB, Malmö, Sweden) in accordance with manufacturer's instructions and with the recommended >25 U/ml cut-off point (53).

Human leucocyte antigen (HLA)-DRB1 genotyping for SE was performed by polymerase chain reaction-based, sequence-specific oligonucleotide probing, as described elsewhere (64). We define the SE as the presence of HLA-DRB1*04 or HLA-DRB1*01, or both. Genomic DNA was isolated from EDTA-preserved blood cells, using a QIAamp Maxi Kit (Qiagen, Chatsworth, California, USA) in accordance with the manufacturer's instructions and stored at -20°C before HLA-DRB1 tissue typing. Serum CRP (mg/l) and ESR (mm/1st hour) were measured using standard laboratory methods.

MRI

Contrast-enhanced MRI were performed before the start of treatment in the 130 patients, who entered the MRI substudy, in conjunction with the clinical, laboratory and radiographic assessments at baseline.

MRI covered the non-dominant wrist in all 130 patients and for 89 patients, in whom the field of view allowed it, also the non-dominant second to fifth metacarpophalangeal (MCP) joints. In patients from the hospitals at Graasten (n=61), Odense (n=21) and Herlev (n=9) a 0.2 T dedicated extremity MRI unit (Artoscan, Esaote Biomedica, Genoa, Italy) equipped with a dual phased array coil was used. In Hvidovre (n=17) and Aarhus (n=22), respectively, 1.0 T and 1.5 T whole-body MRI units (Siemens Impact and Siemens Vision, Erlangen, Germany), both equipped with circular polarised transmit-receive extremity coils, were used. MRI sequences included coronal and axial T1-weighted images (slice thickness 3 mm; matrix 192×192–384) before and after intravenous gadolinium-contrast injection (0.1 mmol gadolinium-DTPA-BMA/kg bodyweight (Omniscan, Amersham Health, Copen-

hagen, Denmark)) and a coronal short tau inversion recovery sequence (slice thickness 3 mm, matrix size 144–182×192–256).

MRI evaluation

The MR image sets were assessed for bone erosions, synovitis and bone marrow oedema according to the OMERACT (Outcome Measures in Rheumatology) MRI scoring system (RAMRIS) (65) by an independent rheumatologist, who was trained in the evaluation of MR images of RA joints. The reader was blinded to the treatment group assignment, clinical, biochemical and radiographic results.

The DANBIO study

The following baseline variables were tested as potential predictors of a good treatment response: Age, HAQ-score, concomitant MTX, concomitant prednisolone, gender, number of previous DMARDs, disease duration. They were entered into a logistic regression model as described in the statistic's section.

ETHICAL CONSIDERATIONS

*CIMESTR*A

All patients gave their written informed consent at the time of inclusion. The written informed consent was renewed before entering the second and the third year of the study. The protocol was approved by the national health authorities and ethic committees (M-1959-98). The trial was performed in accordance with the guidelines for Good Clinical Practice in the European Community. The trial was registered at <http://www.clinicaltrials.gov> (NCT00209859).

DANBIO

DANBIO has been approved by The Danish Data Registry since the year 2000 (j. nr. 2007-58-0014 and j.nr. 2007-58-0006), and since October 2006 as a national quality registry by the National Board of Health (j. nr. 7-201-03-12/1). According to Danish law, informed consent and ethical approval were not required for the present study.

STATISTICAL ANALYSIS

The main statistical analyses that were used for each specific aim are presented here. Further details are presented in the original papers I-VII.

In the CIMESTR study, analysis was by intent-to-treat. At 1 and 2 years, a last observation carried forward approach for missing data was applied. At 5 years, the analyses included all available data from patients who showed up for one or more of the annual (year 3-5) follow-up visits, and no imputation of missing data was done. In addition, completers' analysis (all years), intent-to-treat analysis without the last observation carried forward (year 1 and 2) as well as analysis in which the patients on biologic treatment were excluded (year 5), were also performed.

Comparisons between groups were made with Fisher's exact test for dichotomous responses and the Mann-Whitney U test for nondichotomous responses. Changes over time were analyzed with McNemar's test for dichotomous responses and Wilcoxon's signed rank sum test for non-dichotomous responses.

To adjust for possible demographic and baseline confounders in specific aim 1, a logistic regression analysis was used to compare the odds of an ACR20 response at 1 year. Age, sex, RF positivity, and anti-CCP positivity at baseline were included in the

model. Possible interactions between the treatment group and age, sex, RF positivity, and anti-CCP positivity were also tested.

Longitudinal data analysis of the change in TSS over time (1-2-3-4-5 years) was performed in a linear mixed-effects model with treatment arm, baseline TSS, time and the interaction between treatment arm and time as covariates. The model was tested under condition of unstructured covariance.

Potential baseline predictors (specific aim 2) were initially tested in univariate analyses, secondarily in a linear multiple regression analyses (with delta TSS at 3 and 5 years as dependent variables) and multiple logistic regression models (with delta TSS >0 at 3 and 5 years (yes/no) as the dependent variables).

In the DANBIO studies, data presented are on the study cohorts. We considered the patients who had a registered visit after 12 months of treatment to be representative of all the patients who were still receiving the drug. The LUNDEX factor (Fraction of starters still in the study after x months)X(Fraction responding at x months)(66) was calculated to compensate for the patients who had withdrawn from treatment during the study period (specific aim 4 and 6). The analyses were recalculated with patients treated only with infliximab and on completers only and gave similar results. Differences between groups were analysed using rank statistics (Kruskal-Wallis, Wilcoxon rank sum test, Wilcoxon signed rank test for paired data and the Chi Square test for independence). The Cochran–Armitage test for trend (dichotomous variables), and Jonckheere–Terpstra test for trend (continuous variables) were used (specific aim 4). Adherence to treatment was evaluated by Kaplan–Meier plots and log rank statistics. Logistic regression was used for the prediction model (specific aim 5), stratifying by drug and DAS28 score at baseline.

The probability of response in specific aim 5 and 6 was modelled. The results of these analyses are presented by the odds ratio (OR) with 95% confidence limits (95% CI). ORs for achieving the different treatment responses after 26 and 52 weeks were adjusted for age, disease duration, disease activity, concomitant MTX and prednisolone, number of previous DMARDs, centre and HAQ-score at baseline. The comparison of the drugs was done using logistic regression analysis adjusting for baseline variables as described above. Additional sensitivity analyses included: analyses on unadjusted data; analysis in which all withdrawers were classified as non-responders; analysis including only patients that started treatment after Jan 1st 2003 (at which time adalimumab was marketed), and all gave similar results. No evidence of interaction between the drugs and the covariates (e.g. concomitant MTX) was found. Hazard ratios (HR) were calculated using the proportional hazards model for drug withdrawal. These were corrected for baseline disease activity, age, disease duration, concomitant MTX and prednisolone, number of previous DMARDs, HAQ score and centre. Sensitivity analyses using propensity scores gave similar results (67).

In general, data are reported as the mean (standard deviation (SD)) for variables in which normal distribution was found; otherwise the data are reported as the median (interquartile range (IQR) or range). Categorical variables are presented by frequencies or percentages. P-values less than 5% were considered significant. All data were analyzed by statisticians using SAS (v9.1, SAS Institute, Cary, N.C.) or R (v2.9.0, R Foundation for Statistical Computing, Vienna, Austria)(68).

RESULTS AND DISCUSSION

The results presented in this section reflect the specific aims. More study results are presented in the original papers I-VII.

PATIENT COHORTS

Selected baseline characteristics of the patients in the CIMESTRA and the DANBIO cohorts are shown in table 5.

Table 5. Baseline characteristics of the 2 study populations

	CIMESTRA** (N=160)	DANBIO (N=2326)
Gender (% women)	67	74
Age	52.8 (42.0-62.4)	57.0 (48.0-65.0)
Seropositive disease (%)	66	80
Disease duration (years)	0.27 (0.21-0.38)	8.0 (3.0-16.0)
Ongoing MTX treatment (%)	0	74
Ongoing MTX dosage (mg/week)	0	15.0 (10.0-20.0)
Ongoing prednisolone treatment (%)	0	46
Ongoing prednisolone dosage (mg/day)	0	7.5 (5.0-10.0)
No of previous DMARDs	0	3.0 (2.0-4.0)
Disease activity (DAS28)	5.3 (4.4-5.9)	5.4 (4.7-6.2)
HAQ	1 (0.375-1.500)	1.375 (0.875-1.875)
Erosive disease (%)	61	77*

Unless otherwise indicated, median (IQR) is shown. * Either fulfilled RA criterium “erosive” or x-ray with erosions at baseline
**Some discrepancies compared to III arise from lower N in III, where data were drawn on paired analyses.

The DANBIO cohort had a lower proportion of women, they were older, had higher HAQ score, and more were seropositive for IgM-RF than the CIMESTRA cohort of early RA, which was characterized by very short disease duration, no previous or actual DMARD or prednisolone therapy. The disease activity was high in both groups, with a median DAS28 score around 5.3. These findings reflect the selection criteria for the CIMESTRA and the DANBIO cohorts, with CIMESTRA being an early RA study of DMARD naïve patients, and DANBIO including RA patients with active disease despite MTX and DMARD, just prior to start of treatment with biological agents.

THE CIMESTRA STUDY

Specific aim 1

To investigate short- and long-term (1, 2 and 5 years) clinical and radiographical outcomes after aggressive treatment with methotrexate, placebo-cyclosporine/ cyclosporine and intraarticular betamethasone in patients with early RA participating in the CIMESTRA study (paper 1, 2 and 3)(1-3).

The proportion of patients achieving an ACR20 response at 1 year was higher in the combination therapy group than in the monotherapy group (85% vs. 68%, respectively, p=0.02). At 2 years it was 88% vs. 73% (p=0.04) and at 5 years 94% vs. 85% (NS). Similarly, the proportion of patients achieving ACR50 and

ACR70 responses were consistently higher for the combination therapy group than for the monotherapy group, but this did not reach statistical significance except for ACR50 after 2 years (79% vs. 62%, $p=0.03$). At 5 years a total of 81% and 67% had achieved ACR50 and ACR70 responses, respectively (NS between groups).

ACR remission at 1 year was achieved by 35% in the combination therapy group and 28% of the monotherapy group, $p=0.39$. At 2 years it was 41% and 35%, respectively (NS), and at 5 years it had increased to 60% and 52%, respectively (NS between groups). A total of 28 and 27%, respectively, were in sustained remission at 5 years. The proportion of patients achieving DAS28 remission at 1 year was 43% and 34% in the combination therapy group and monotherapy group, respectively, $p=0.33$. This increased to 51% and 50%, respectively, at 2 years and to 80% and 76% at 5 years.

The estimated yearly rate of progression in the TSS was mean 22 (median 5; IQR 0-32) for the combination therapy group; and mean 16 (median 11; IQR 0-21) for the monotherapy group. The increases in TSS from baseline to 1, 2 and 5 years were mean 0.78, 1.42 and 4.09 (median 0, 0, 1.5), respectively, in the combination therapy group. For the monotherapy group, it was mean 1.12, 2.03 and 4.92 (median 0, 0, 1), respectively. There were no differences in radiographic progression between the two treatment groups at any time point. This was confirmed in the linear mixed-effects model that included all available radiographic data up to 5 years, and showed that treatment group and its interaction with time were not significant, whereas time and baseline TSS were (data not shown). At baseline, 61% of the patients had erosive disease (TSS>0), while corresponding values after 1, 2 and 5 years were 64%, 66% and 77%. The mean annual progression rate was 0.90 after 5 years.

The present study was to our knowledge the first study with maintained double-blinding and a standardized treatment protocol during 5 years' follow-up in early RA patients treated with DMARD. It showed that aggressive DMARD treatment including intra-articular betamethasone aiming at strict synovitis suppression lead to sustained excellent disease control both clinically and radiographically. Addition of cyclosporine during the first 2 years improved the clinical responses markedly after 1 and 2 years, but had no impact on the progression of joint destructions. Initial MTX monotherapy was as effective as initial MTX and cyclosporine combination therapy with respect to clinical and radiographical outcome at 5 years.

At 5 years, more than 75% of patients were in DAS remission, more than 50% were in ACR remission and more than 25% had achieved sustained remission (defined as ACR remission at both year 3, 4, and 5). Compared to the COBRA trial, the average DAS28 scores from year 3 to 5 were 50% lower in the present study (69). ACR remission rates in the Fin-RACo study were half of what was achieved in the present study (70). The results matched those reported in RCTs of biologic therapies in RA at an early stage of the disease (71-73). One in six patients had been able to withdraw from therapy altogether after ≥ 12 months' ACR remission. Less than 20% had switched to biological agents, although the follow-up period took place during an era of widespread use of biological treatments.

Radiographic progression was effectively halted by the present treatment strategy. Thus, almost 50% of the patients did not progress radiographically during 5 years, and the TSS increased on average by less than 1 unit per year.

Since the treatment strategy of strict synovitis suppression was applied to both treatment arms throughout the study period, the isolated impact of initial combination therapy could

be studied. This is in contrast to most other long-term (i.e. > 2 years) follow-up studies of combination therapy in early RA, which had either an open design or the treatment arms differed with respect to other factors, such as visit frequency or use of concomitant prednisolone (74-77). In the present study, we found that although the combination therapy group had better clinical outcome regarding ACR20 during the first years, there was no clinical or radiographic benefit from combination therapy during long-term (5 years') follow-up.

The annual progression rate in the combination therapy group at 5 years was 5.6 units versus 8.6 units in the sulphasalazine group in the COBRA trial, and only 12% in the COBRA trial had no radiographic progression after 5 years follow-up (69). In the Fin-RACo study, radiographic progression was lowest in the combination therapy group, but considerably higher than in the present study, although direct comparison is complicated by the fact that radiographic damage was assessed by Larsen score (70). Since both studies compared sulphasalazine in monotherapy with combination therapy, they do not shed light on whether MTX as first line drug should be given alone or in combination with other DMARDs. A study of 145 patients with early RA found that patients who had received MTX, sulphasalazine or both during the first year had similar clinical, functional and radiographical status at 5 years with open-label, free-choice follow-up treatment (74). In the BeSt study, which is an unblinded study of early RA, the mean progression in TSS was 6.7 in the initial combination therapy group and 11.7 in the monotherapy group at 4 years. Whether this should be attributed to sulphasalazine and hydroxychloroquine or to the initial high-dose prednisolone given to the patients in the combination therapy group cannot be decided due to the study design (78). In patients with early RA treated with TNF α blockers, even more effective halting of radiographic progression has been achieved (71-73).

MTX was chosen as first-line therapy because of its proven effectiveness and acceptable toxicity and in accordance with international treatment guidelines (25;79;80). A study that was published during the development of the CIMESTR study demonstrated that additional cyclosporine lead to increased clinical efficacy (30), and later studies showed that the combination of MTX and cyclosporine had a positive impact on radiographical progression (31) and altered the pharmacokinetics of MTX beneficially (81). Consistent with another study of combined cyclosporine and MTX treatment in early RA, cyclosporine was given in a low-dose regime (36). In contrast to that study, MTX dosage was increased primarily rather than the cyclosporine dosage. This strategy turned out to have few and acceptable side effects. Since 1998, when the CIMESTR trial was initiated, the combination of cyclosporine and MTX has not been embraced by the rheumatological community with reference to its toxicity. The present study demonstrated that in a low-dose (2.5mg/kg), short-duration schedule with close monitoring of serum creatinine and blood pressure, there was no evidence of sustained side effects from cyclosporine. The present study showed, however, that although cyclosporine to some degree improved the clinical responses for as long as it was given, it did not at any time point influence radiographic progression.

Glucocorticoids are effective as bridging therapy, since they rapidly relieve signs and symptoms of RA. Intra-articular administration ensures a high concentration of glucocorticoids at the site of inflammation and reduces synovitis more than MTX alone, has been used successfully in other studies of early RA (36;75;82). In the present study the cumulative dose was moderate. There were few adverse events to the intra-articular injection.

tions of betamethasone, and the use of intra-articular injections was in no cases the reason for withdrawal from the study. The very modest use of glucocorticoids during the extension period supports the efficacy of the treatment strategy.

Addition of hydroxychloroquine during the second year may have increased the potency of MTX, since coadministration of MTX with hydroxychloroquine has been reported to increase the bioavailability of MTX compared to MTX administered alone (83).

The present study showed that aggressive treatment with MTX aiming at suppression of synovitis with intra-articular betamethasone injections on demand lead to remission and halted radiographic progression in the majority of patients after 5 years. Further it showed that initial treatment with MTX in combination with cyclosporine was not superior to initial MTX monotherapy regarding long-term clinical response and radiographic progression.

Specific aim 2

To identify which baseline factors that were predictive of radiographical progression after 2 and 5 years in the CIMESTRA study (paper 3 and 4)(3;4).

In univariate analysis, baseline TSS, MRI bone marrow oedema score (wrist or wrist-and-MCP) and MRI erosion scores (wrist or wrist-and-MCP) were significantly associated with radiographic progression (delta TSS) at 2 years. In multiple linear regression analysis after backward selection, only baseline MRI bone marrow oedema score (wrist or wrist-and-MCP) remained in the final model with delta TSS at 2 years as the dependent variable. At 5 years, baseline wrist MRI bone marrow oedema score, TSS and anti-CCP were all independent predictors of radiographic progression. Wrist MRI bone marrow oedema score explained 25% of the variation in radiographic progression (Pearson's $r=0.50$) at 2 years, and this was largely unchanged at 5 years (23%, $r=0.48$). Additional sensitivity analyses with logistic regression analysis (with radiographic progression (yes/no) at 2 years as the dependent variable) were performed and gave similar results. At 5 years, baseline MRI bone marrow oedema was borderline significant (OR=1.44 (95%CI: 0.95-2.20, $p=0.09$), whereas anti-CCP (OR=4.03 (1.65-9.82), $p=0.002$) and TSS (OR=1.12 (1.03-1.21, $p=0.006$) were independent predictors.

To our knowledge this randomized, clinical trial was the first that investigated a panel of potential prognostic markers including MRI and had long-term follow-up of radiographic progression. The panel included imaging (conventional x-ray and MRI), immunologic (anti-CCP, IgM-RF and IgA-RF), environmental (smoking, educational level), genetic (shared epitope) and disease activity markers. Among this panel of markers, MRI bone marrow oedema was the strongest independent predictor of progression in radiographic changes 2 years later in patients with early RA. In the prediction of radiographic progression at 5 years, anti-CCP and TSS were also predictors in addition to MRI bone marrow oedema.

The study expands the results of previous studies (52;84-89). MRI studies have investigated the predictive value of MRI after 1, 2, 6 or 10 years of follow-up (84-86;89) and found it to be a predictor of radiographic erosions.

In contrast to previous studies, which were all done in a single-centre design, the present study was performed on different MRI units, including low-field (0.2 tesla) and 1.5 tesla units. It may be considered a disadvantage, but was unavoidable due to

the multi-centre design with different units at the different hospitals. Methodological studies have reported that the sensitivity for detecting bone marrow oedema may vary with different types of MRI units (90). In the present study, 70% of MRI scans were done using a low-field dedicated extremity MRI unit, which is less sensitive than high-field units. This may have weakened the "signal" of MRI as a prognostic marker, but on the other hand also makes the study more generalizable to other populations and indicates that MRI bone marrow oedema is a robust predictor of radiographic progression.

MRI bone marrow oedema has in established RA been shown to represent inflammatory infiltrates in the bone marrow (91;92). In contrast to radiographic erosions, which reflect bone damage that has already occurred, bone marrow oedema thus may represent an important part of the early immunopathologic development in RA (91).

The finding that regional MRI (wrist or wrist-and-MCP) predicts radiographic progression in other anatomical regions (both hands, wrist and forefeet) confirms previous studies (52). As expected, the predictive value was highest for MRI of both wrist and MCP joints in comparison to MRI of wrist alone. Scanning of MCP joints was however only feasible in some patients because of the limited field of view in some scanners.

All previous MRI studies, except one (89), were imaging studies that did not include anti-CCP or take into account other potential prognostic markers such as smoking and shared epitope. Since the most significant predictor of disease outcome in RA is the treatment (93), studies performed within a standardised treatment protocol have been lacking. Thus, all previous studies have been without a standardized treatment regime.

A recent meta-analysis concluded that anti-CCP positive RA patients had greater risk of radiographic progression than anti-CCP negative patients (53). The reviewed studies only included a limited number of variables besides anti-CCP antibodies and RF, and none included MRI. In the present study, anti-CCP was a significant predictor of radiographic progression after 5 years, but not after 2 years. This may, at least in part, be explained by the tight disease control and low rate of radiographic progression, which left little power to discriminate associations with radiographic changes. Baseline TSS was also a predictor at five years. This is in accordance with other studies, e.g. one study of early RA, in which the baseline erosive score was the most significant prognostic marker of radiographic progression after two years, followed by anti-CCP positivity and elevated ESR (94). Another study reported anti-CCP and CRP to be the only significant baseline predictors of radiographic progression after 10 years (95). It should be noted that these studies were done during a time period with far less intensive treatment than in the present study. Thus, many patients were without DMARD treatment, and of those receiving DMARD, MTX was only given in a minority. That resulted in a median progression in TSS of 8 units after two years (94) and 46 units after 10 years (95), thus reflecting poorer disease control than by today's treatment strategies. A recent study of 238 patients with early RA showed anti-CCP to be the strongest independent predictor of radiographic progression after 10 years (96). Also in that study, radiographic progression was higher (almost 3 units per year) than in the present.

HLA-SE is associated with the presence of anti-CCP antibodies in early RA, and seems to play an indirect role as a risk factor for erosive disease (97). A mortality study of patients with early RA showed that patients with DRB1*0101/0401 genotype had more radiographic progression after 2 years compared with all other genotypes than DRB1*0401/0401 (98). HLA-DRB1-SE was

not found to be a prognostic marker for erosive disease in the present study, which may be due to the limited radiographic progression, although a previous study showed similar results (99).

Smoking is a well-known risk factor for developing RA, but its influence on RA disease progression needs further investigation. Two recent studies supported the present study and reported that smoking status did not influence radiographic progression in early RA after 2 years (100) or in RA patients with variable disease duration (101).

The present study indicates that MRI could be a useful supplement to the conventional examination programme in early RA patients, in order to optimize the identification of patients at high risk of erosive progression.

DANBIO

Specific aim 3

To evaluate the registration of serious adverse events and adverse events in patients treated with anti-TNF drugs during the first 2 years of post marketing clinical use based on DANBIO data (paper 5) (5).

During the first 2 years of registration of biological agents in Danish patients with inflammatory arthritis, a total of 448 treatment series (419 individuals) were registered with a median follow-up time of 39 weeks. The patients received either infliximab (87%) or etanercept (13%), and the cumulated years of treatment for the 2 drugs were 279 and 64 years, respectively.

A total of 47 SAEs (in 42 individuals) and 544 AEs (affecting 229 individuals) were reported to the DANBIO registry during this period of time. During the same period 30 SAEs and 23 AEs were reported to the Danish Medicines Agency. The median time-on-drug when the SAE occurred was 23 weeks (0-126 weeks). The frequencies of SAEs and AEs were 12.5 and 180 per 100 treatment years with no difference between the two drugs.

Of the SAEs, hypersensitivity/infusion reactions were the most prevalent (N=20), followed by infections (N=14), cardiologic symptoms (N=3), malignancy (N=1) and miscellaneous (N=9). No cases of tuberculosis were reported during this period. Two deaths occurred, they were considered unrelated to the treatment.

The frequencies of AEs per 100 treatment years were: Infections (102) (including bacterial (42), viral (56) and fungal infections (3)); exzemas (65); hypersensitivity/allergic reactions (6); lupus-like symptoms (6).

In univariate logistic regression analysis, significant risk factors for bacterial infections were high age, long disease duration and many previous DMARDs. In multivariate analysis none of these risk factors reached statistical significance.

Reliable systematic registration is of major importance in obtaining knowledge about adverse events in the use of biological – and other – treatments in routine care. During the first 2 years of post-marketing use, the voluntary registration of patients in DANBIO picked up twice as many SAEs and almost 20 times as many AEs compared with the mandatory reports to the Danish Medicines Agency.

The frequencies and types of SAEs and AEs were comparable to those that had been reported in clinical trials (102-105) and post-marketing registries (45;46) by the time the study took place.

In conclusion, the regular registration of patients in the DANBIO registry improved the reporting of SAEs and AEs in rheumatologic patients receiving biological treatment.

Specific aim 4

To investigate whether changes in prescription practice in patients with rheumatoid arthritis treated with biologics affected treatment response and adherence to therapy based on DANBIO data (paper 6) (6).

From the year 2000/2001 cohort to the year 2005 cohort, a decrease in baseline disease activity was observed (from 5.9 (IQR: 5.0-6.6) to 5.3 (4.5-6.0), respectively, $p<0.001$). Similarly, reductions in the previous number of DMARDs (4 (3-6) to 3 (2-4), $p<0.001$), fraction of patients receiving concomitant MTX (81% to 71%, $p<0.001$) or prednisolone (66% to 41%, $p<0.001$) as well as dose of prednisolone (10 mg (5-10) to 7.5 mg (5-10), $p<0.001$) were seen between 2000/2001 and 2005. During the same period the median age of patients increased (from 55 years (45-62) to 58 (48-66)), as did the dose of methotrexate (from 12.5 mg/week (7.5-15.0) to 20 mg/week (12.5-25)), whereas disease duration was unchanged (from 10.0 years (5.0-16.0) to 9.0 years (3.0-16.5)), ($p=0.13$). An increasing number of patients started treatment with etanercept and adalimumab at the expense of infliximab. Thus the fraction of patients that received infliximab as the first biological treatment decreased from 87% to 34% ($p<0.001$) during the period.

During the same period, the DAS28 improvement after 1 year increased from 1.8 to 2.2 units, $p<0.001$. The percentage of patients with a good EULAR response increased from 28% to 50% ($p<0.001$), whereas the fraction with no response declined from 29% to 16% ($p=0.001$). After correcting for the patients who had withdrawn, the EULAR responses were lower, but the patterns were similar.

Similarly, the fraction of patients who had achieved an ACR20 response after 1 year of treatment increased from 53% to 69% between 2000/2001 and 2005, $p<0.001$. Also ACR50 (31% to 51%, $p<0.001$) and ACR70 responses (13% to 30%, $p<0.001$) increased. Of all patients who started treatment with biological agents, including withdrawers, 43% achieved an ACR20 response, 30% and ACR50 and 16% an ACR70 response when looking at the whole period. The withdrawal rate after 1 year ranged from 27% to 38% with no trend over time.

The present study documented that despite a change in prescription practice during the period from 2000 to 2005 towards less disease activity at the time of treatment initiation, the efficacy of the treatments improved over the years as evaluated by DAS changes in absolute numbers, EULAR responses and by ACR treatment responses. Thus, in patients who started treatment in 2000/2001, about 1 in 4 would achieve a good treatment response after 1 year, and this had increased to approximately 1 in 2 patients who started treatment in 2005. Similarly, the fraction of patients achieving an ACR70 response increased from being 1 in 8 patients to 1 in 3. Patient selection for biological treatment might have biased the response rates in the first years of post-marketing use, with many cases of longstanding, partly burnt-out disease. However, the trend for improved response seemed to continue also in the later years. One may hypothesize whether the development of the DANBIO registry may have contributed. In year 2000, the registry was paper-based with no feedback to the treating physician. From around year 2002, treatment responses were returned to the treating physician at

irregular intervals and with approximately 3 months' delay. In 2004, the web-based solution was launched and gradually the systematic real-time feedback was integrated in the routine care of patients across the country. It could also be argued that the increasing number of available TNF inhibitors may have led to an increased likelihood of switching between biological agents, resulting in an improved treatment response. However, the present study included only the first course of biological drug, and we found that the drug survival was largely unaffected by the year of treatment initiation. Furthermore, calculations on only the patients receiving infliximab gave similar results.

It is remarkable that during the same period, the fraction of patients that received concomitant prednisolone was reduced from 66% to 41%. The impact of concomitant MTX is unclear: the fraction of patients on MTX declined from 81% in the 2000/2001 cohort to 71% in the 2005 cohort, whereas the median MTX dosage nearly doubled from 12.5 mg to 20 mg weekly.

RCTs of the three TNF α blockers in populations resistant to MTX monotherapy have shown that ACR50 responses are achieved in 21-69% of patients (104;106;107), and two meta-analyses concluded that the efficacy of the TNF inhibitors does not differ significantly (108;109). Two population-based studies suggested that the response rates of anti-TNF treatments in routine care as judged by ACR20, ACR50 and ACR70 responses were smaller than in RCTs (110;111). Our findings did not support this, since we found ACR50 to be achieved in 43% of completers.

There are only few reports of efficacy of biological drugs outside clinical trials. In Sweden, a good EULAR response was seen in 33-35% of 949 patients at 12 months, which is of a magnitude similar to our findings (66). Similarly, in 120 British patients who received infliximab, 48% achieved a good EULAR response after one year (112). In a Swiss study, in contrast, the improvement in DAS28 was only 0.60 units compared with 1.8 in the present study (113). The finding was supported by a EULAR good response of only 10% in the Swiss study in comparison with 26 to 49% in the present study. The reasons for this remarkable difference are not known.

One-year adherence to therapy has been reported to be 60 to 80% (66;113-115), which is in accordance with the present findings.

In conclusion, this was the first nationwide documentation of the efficacy of biological agents in patients with RA treated in standard care. From 2000 to 2005, significantly improved treatment responses to TNF α blockers were observed in clinical practice.

Specific aim 5

To identify which baseline factors that were predictive of a good treatment response after 6 months in RA patients treated with biological drugs in clinical practice based on DANBIO data (paper 7)(7).

After 6 months, an ACR70 response had been achieved in 19%, good EULAR response in 41%, DAS remission in 25%, and CDAI remission in 13% of the patients who had not withdrawn. High age (OR=0.79 (95%CI: 0.71-0.87) per 10 years increase), high HAQ score (OR= 0.86 (0.75-0.98) per 2-fold increase) and concomitant prednisolone (OR 0.69 (0.53-0.90)) were independent, negative predictors of an ACR70 response, whereas concomitant MTX, male gender, number of previous DMARD treatments and disease duration were not.

For all outcome measures, the patterns were largely similar, with statistically significant ORs <1 for high age, high HAQ

score, concomitant prednisolone and many previous DMARDs, OR around 1 for male gender and disease duration, and ORs>1 for concomitant MTX (only statistically significant for EULAR good response).

Thus, in the present study, high age, low functional status and concomitant prednisolone were negative predictors for an ACR70 treatment response. In other observational studies of TNF α blockers, low functional status was also associated with poorer response (55;56), whereas the present study is the first to report higher age and concomitant prednisolone to be associated with treatment response to TNF α blockers. Concomitant MTX has been reported to be a positive predictor in one, but not in another study, and we found only an association between MTX and treatment response regarding the EULAR good response (55;56). The association between concomitant prednisolone and treatment response may be explained by the flexible dosing regime in routine care: Patients who receive prednisolone at baseline because of severe disease, typically reduce the dose once the biological agent becomes effective, and this reduction will, other things being equal, lead to more disease activity.

Specific aim 6

To investigate and compare the treatment responses, remission rates and drug adherences in RA patients treated with adalimumab, etanercept and infliximab in clinical practice based on DANBIO data (paper 7)(7).

The patients who received the three TNF inhibitors were similar regarding age, gender, disease activity and disease duration at baseline, but fewer patients treated with etanercept received concomitant MTX (61% vs. 70% for adalimumab and 87% for infliximab), and more patients receiving infliximab were on concomitant prednisolone (50% vs. 40% for adalimumab and 43% for etanercept patients).

Overall, the crude treatment response rates after 6 and 12 months were highest for adalimumab, intermediate for etanercept, and poorest for infliximab. After LUNDEX correction, 19% of adalimumab, 17% of etanercept and 11% of infliximab patients had achieved ACR70 at 6 months. A total of 41%, 34% and 27% had a good EULAR response. Similarly, 26%, 21% and 17% were in DAS28 remission, and 15%, 10% and 8% in CDAI remission after 6 months, respectively.

After correction for differences in baseline parameters (gender, age, disease duration, seropositivity, DAS28, concomitant MTX and prednisolone, number of previous DMARDs, HAQ score and centre), the OR for achieving an ACR70 response after 6 months of treatment were 2.05 (95% CI: 1.52-2.76) for adalimumab and 1.78 (1.28-2.50) for etanercept with infliximab as the reference drug. There was no significant difference between adalimumab and etanercept (OR 1.15 (0.82-1.60) with etanercept as the reference). The ORs for adalimumab versus infliximab ranged from 1.78 to 2.76 and were statistically significant for all outcome measures (ACR70 and ACR50 treatment responses, good or good/moderate EULAR response, DAS remission, CDAI remission). For etanercept versus infliximab, the ORs ranged from 1.16 to 1.99, and were statistically significant for all outcomes except DAS28 remission and CDAI remission. For adalimumab compared with etanercept, the ORs ranged from 1.15 to 1.58 and were significant for EULAR good response and CDAI remission.

For adalimumab, the first dose was average 40 mg (SD 2 mg), the maintenance dose was 40 mg (2mg), maintenance frequency (weeks' interval) was 1.9 weeks (0.5 week) and the dose at the last visit was 40 mg (3 mg). For etanercept, the correspond-

ing values were: 45 mg (10mg), 45 mg (11 mg), 0.9 weeks (0.3 weeks) and 44 mg (11 mg), respectively. For infliximab (average body weight 72.6 kg): 229 mg (55 mg), 257 mg (84 mg), 6.9 weeks (1.6 weeks) and 259 mg (87 mg), respectively.

The annualized maintenance dose was for adalimumab: 1099 mg (9.5 mg) (mean (SE)), etanercept: 2533 mg (6.2 mg), infliximab: 1949 mg (40 mg). The corresponding standard maintenance dosages were: 1040 mg, 2600 mg and 1417 mg (assuming 6.5 treatments of infliximab per year), respectively.

In patients that had a recorded dosage for the first and the last infusion (n=591), the dosage of infliximab at the time of withdrawal was investigated. In total, 51% of patients who withdrew due to LOE after week 26 were on increased dosage corresponding to on average 169% of standard dosage. This corresponds roughly to increasing the dosage from 3 to 5 mg/kg or to decreasing the intervals from every 8 weeks to every 5 weeks.

The unadjusted drug adherence rates at 4 years were: adalimumab: 52% (95% CI: 46-57%); etanercept: 56% (51-62%); and infliximab: 41% (37-44%), $p < 0.0001$. The HRs for drug withdrawal (regardless of reason for withdrawal and adjusting for baseline DAS28, age, disease duration, seropositivity, concomitant MTX and prednisolone, number of previous DMARDs, HAQ score and centre) were 1.35 (95% CI 1.15-1.58) for infliximab versus adalimumab, 1.98 (1.63-2.40) for infliximab versus etanercept and 1.47 (1.20-1.80) for adalimumab versus etanercept.

This study was the first to compare directly the efficacy of adalimumab, etanercept and infliximab with regard to their ability to elicit treatment responses that reflect modern treatment goals including remission. The main finding was that in DMARD treated, TNF α blockers naïve RA patients, ACR70 treatment responses and remission rates were lowest for infliximab, intermediate for etanercept and highest for adalimumab. The findings persisted after correction for a large number of confounders and various sensitivity analyses (including analyses on unadjusted data, analysis in which all withdrawers were classified as nonresponders, and analysis including only patients who started treatment after January 1st 2003), and were consistent across different outcome measures and different follow-up times.

Effectiveness of treatment was assessed by treatment responses (ACR70 and good EULAR response) and by proportions of patients achieving remission (DAS28 or CDAI remission). Adjusted for differences in baseline characteristics, the ORs for any of the selected treatment responses or remission criteria were 1.8 to 2.1 for adalimumab and 1.2 to 1.8 for etanercept (with infliximab as the reference drug), and 1.2 to 1.6 for adalimumab versus etanercept. Drug retention rates, which may be considered a surrogate marker for drug efficacy, were lowest for infliximab, intermediate for adalimumab and highest for etanercept. The differences in clinical efficacy persisted after adjustment for withdrawers.

Few studies have attempted to compare the efficacy of the individual TNF α blockers. All RCTs of efficacy have been funded by the pharmaceutical industry, and no head-to-head RCTs have been published. A limited number of adjusted indirect comparisons of RCTs have been done, but with inconclusive results (108;116-118). A meta-analysis including 26 placebo-controlled RCTs of RA patients in MTX resistant populations, were not able to show any difference in efficacy among the 3 TNF α blockers (108). It should be noted that the confidence intervals of the risk ratio estimates were so wide that clinically significant differences might have been missed. Another study suggested that etanercept might be more efficacious than both adalimumab and infliximab, but this study also lacked statistical power (116). A

third study found a tendency towards lower efficacy for etanercept (compared with MTX) than for infliximab and adalimumab (in comparison with MTX), but the selection of patients for etanercept (partly MTX naïve) was different from that of the other drugs (MTX resistant), which hampers the results and illustrates that comparisons between RCTs have potentially significant flaws (118). A recent meta-analysis concluded that all TNF α blockers were not different from each other (117). Latest a Cochrane review of all previous Cochrane reviews on RCTs of biological agents presented ratio RR estimates, which suggested that adalimumab and etanercept were more efficacious than infliximab, but it did not reach statistical significance (119).

Observational studies of cohorts of unselected patients receiving standard clinical treatment allow direct comparisons of the drugs, although the lack of randomization should be kept in mind in the interpretation of results. A Dutch study of 770 RA patients (120) reported that infliximab performed poorer than adalimumab and etanercept (which performed equally well) with regard to achieving a moderate-good EULAR response as well as drug survival. This contrasts to the present study, in which adalimumab had a significantly better outcome than etanercept regarding EULAR good response, and better retention rates of etanercept than of adalimumab. It was, however, not specified in the Dutch study, which potential baseline biases that were adjusted for, and it did not include strict response criteria such as ACR70 or EULAR good treatment responses or remission rates.

Drug retention rates were overall lower for infliximab than for adalimumab and etanercept. It was most pronounced for withdrawal due to adverse events (HR 1.8-2.7), but also significant for infliximab compared with etanercept in patients who withdrew due to lack of efficacy. A recent Swiss study reported poorer drug survival for infliximab, mainly due to an increased risk of adverse events (121). They reported a drug survival of infliximab that is similar to the present study with a half-life of approximately 2 years. In contrast, the present study found overall higher retention rates for etanercept compared with adalimumab and infliximab regardless of the reason for withdrawal. A French study of 304 RA patients support this finding (122). A Swedish study reported higher adherence rates in etanercept-treated patients than infliximab-treated patients, and etanercept tended to have better treatment response, although the finding was not consistent (66). In an early study from the German registry, short-term drug survival rates were similar for etanercept and infliximab (115).

The observational design of the present study has weaknesses. Lack of randomisation and blinding may have resulted in e.g. bias by indication, channelling bias and performance bias. However, no clinically significant differences in disease duration or disease activity were seen at baseline, and the results were robust in a variety of sensitivity analyses. In addition, CRP, which is an objective disease marker, decreased less in infliximab-treated patients than in adalimumab-treated patients. It cannot be excluded that differences in the timing of clinical assessment may have biased the treatment outcomes, since infliximab-treated patients were scored on the day of infusion (at trough drug levels), whereas the subcutaneously treated patients were scored independently of the day of treatment. Furthermore, infliximab dosage may have been insufficient in some patients, and that higher dosages might have improved the outcome. However, the patients were treated according to standard recommendations, and the infliximab dose had been increased in 69% of patients compared to standard in the majority of patients that withdrew due to lack of efficacy. Furthermore, the higher

hazard ratio for withdrawal for infliximab compared with adalimumab and etanercept support the findings, and this ratio is independent of differences in timing of clinical assessment.

In conclusion, significant differences were found in efficacy and adherence to therapy of adalimumab, etanercept and infliximab. Infliximab had the lowest treatment responses, remission rates and drug adherence rate. Adalimumab had highest treatment responses and remission rates, whereas etanercept had longest drug survival rates. The findings were consistent across outcome measures and sensitivity analyses.

GENERAL DISCUSSION

RANDOMIZED CONTROLLED TRIALS AND OBSERVATIONAL STUDIES

The development of improved treatment strategies is often based on RCTs that provide evidence-based knowledge on both DMARDs and biological agents. However, since RA is a chronic, often life-long, disease, and it is difficult to retain patients in RCT protocols for more than a couple of years, observational prospective RA cohorts have increasingly been established and delivered long-term data on RA patients and their treatments. RCT and observational studies are thus complimentary, and both are required to improve our understanding and management of RA (123;124). Each have strengths and weaknesses, some of which are listed in table 6. Double-blinded, placebo-controlled RCTs have the inbuilt advantage of eliminating a variety of potential biases (e.g. preference bias, channeling bias, selection bias, performance bias). Observational studies are by nature open and not randomized. With large number of patients in observational studies, one can try to compensate and control for a number of factors that may affect the outcome e.g. gender, age, disease activity, disease duration, but outcomes should be interpreted with care.

Table 6. Strengths and weaknesses of RCTs and observational studies

	Randomized controlled trials	Longitudinal, observational cohorts and registries
Strengths	Randomisation Comparison with placebo Double-blinding	Long follow-up Reflects routine care Generalizability Large numbers of patients Detection of rare/long-term adverse events Relatively cheap to conduct
Weaknesses	Selection bias Short follow-up Smaller numbers of patients Low generalizability Expensive (Inflexible regimens)	Biases (selection, preference, performance, channeling etc) Lack of randomization Lack of/not optimal group of controls Varying follow-up times

On the other hand, the observational studies represent real-life patients, with a broader spectrum of disease course and

outcome than the RCTs, and they are typically followed-up for longer periods of time, sometimes for decades. They allow for greater generalizability, although it should be kept in mind that for both RCTs and observational studies, potential sources of biases include left censoring (milder RA not being referred to secondary care) and right censoring (severe RA not surviving long enough for follow up or too ill to participate) (125). Results from RCTs may be hard to generalize, since up to 50% of routine care patients cannot be included due to restrictions based on e.g. age, comorbidities, disease activity, and concomitant drug therapy (6;110;126). Thus, differences in results reported from RCTs and observational studies are not uncommon (127).

The flexibility of treatment regimens is often limited in RCTs with carefully defined criteria for dose increases and explicit rules for withdrawal of medications. In observational studies, in contrast, dose changes and switching of therapy reflect the clinical judgment of treatment efficacy that may vary from patient to patient and between departments (123).

Observational studies allow for comparison of drugs that would never be set up in a RCT and thereby become a source of identifying potentially important differences in terms of efficacy and safety e.g. between TNF α blockers (7;110;128-131).

KEY OUTCOMES – CHALLENGES AND PITFALLS

In RCTs of patients with RA, three key outcomes are usually assessed: 1) Changes in signs and symptoms of inflammatory arthritis, usually termed “disease activity”, and assessed by changes in DAS28 score (EULAR response) or by ACR treatment responses (ACR20, 50 and 70); 2) progression of disability, assessed by the HAQ, and 3) erosive damage, assessed on x-rays using standardized scoring systems such as the Larsen or the Sharp/modified Sharp scores (132).

In observational studies, the same key outcomes should ideally be assessed. However, real-life patient care is not being subject to the same strict monitoring as RCTs are, and budgets are lower. Therefore, one or several of the outcome measures may be omitted in observational studies, e.g. the BIOBADASER registry was established for the surveillance of adverse events and does not include assessment of disease activity.

In the present studies, these differences were also apparent: In the CIMESTRA study, a wide range of baseline and outcome variables was included and all of the 3 above-mentioned were reported in the publications. In the DANBIO project, DAS28 and HAQ were both assessed longitudinally on a routine base, whereas x-rays were not collected for systematic and standardized scoring. Therefore, no results on the latter have been published so far. However, there is an ongoing initiative aiming at collecting serial radiographs in DANBIO patients receiving biologics (60;61). The spontaneous registration of SAEs is efficacious (5), but so far the main focus of publications have been on drug efficacy.

In the CIMESTRA trial, all results were analyzed and presented on an intention-to-treat principle. This is a common strategy in RCTs, selected to avoid overemphasizing the impact of the active treatment (here: Cyclosporine and MTX combination therapy). However, there is a risk that patients in the placebo-cyclosporine and MTX monotherapy group, who failed on the placebo treatment and were excluded from the study, and afterwards received more intensive treatment, e.g. were started on biologics, would lead to an overestimation of the benefits of placebo therapy (MTX monotherapy) (132). The ITT analysis is thus conservative, leading to an increased risk for a type II error.

However, additional completer's analyses were also performed and reassuringly gave similar results.

Observational studies face similar challenges with patients who either withdraw from therapy (and drop out of registration) or are not being followed-up despite continuous treatment. We addressed the former problem by calculating LUNDEX corrected outcomes, thereby adjusting for the patients who had withdrawn from therapy. Regarding the patients with missing data, the assumption was made that these no-shows were not different from the patients who showed up. This assumption is most likely not correct (e.g. one might expect no-shows to have either very severe or very mild disease activity compared to show-ups), but lack of alternative made this the only practicable solution.

The relatively long follow-up time in both studies also put another issue into focus: The impact of time on the key outcome variables (132). This is illustrated in the CIMESTRA study, in which a significant difference in clinical response between the two treatment arms was demonstrated after one and two years, but not after 5 years.

TREATMENT STRATEGIES IN RA

This chapter will discuss some key aspects of modern treatment strategies in RA based on our own studies as well as the present literature. Non-pharmacologic treatment of RA, the use of analgetics, comorbidities including cardiovascular disease and osteoporosis, and switching between biological treatments are topics that lie outside the scopes of this thesis.

RA has a major impact on many areas of patients' lives. At any stage of the disease, joint damage with subsequent permanent disability may occur, and all treatments should aim at reducing the joint destructions. Among the factors that have the greatest impact on prognosis in rheumatoid arthritis, pharmacologic intervention is probably the most significant. Treatment strategies have changed dramatically during the last decades from a concept of symptom control (with the rheumatologist in a "reactive" position) to one of disease control, in which the rheumatologist is proactive and aims at bringing the patient into remission, i.e. without any sign of the disease being active. This shift is the result of several significant advances in the field including a goodbye to toxic or non-efficacious DMARDs, the use of MTX as the anchor drug in RA treatment, better designed and conducted RCTs, and biologic agents that have high efficacy, but also a potential for severe side effects and in addition represent a substantial burden on economic resources in health care systems.

Early or delayed treatment with DMARDs

The principle of early treatment is based on the concept of a therapeutic window of opportunity early in the disease (133;134). By acting in this window, it is assumed that one gets a short-term effect of better treatment response and a long-term effect altering the disease permanently to a milder course. Even a delay of 8 to 9 months in starting DMARD therapy has a significant impact on disease parameters years later (134).

In a meta-analysis of 12 studies, this issue was addressed (135). The pooled estimate of effects from the studies demonstrated a significant reduction of radiographic progression in patients treated early, with a standardized mean difference of -0.19, which corresponded to a 33% reduction in long-term progression rates compared with patients treated later. Patients with more aggressive disease seemed to benefit most from early DMARD initiation. It was concluded that the effect size from early DMARD initiation was almost half the effect size observed from

MTX therapy, and that it was sustained for several years regardless of subsequent treatment.

This is an impressive impact and strongly supports the importance of early intervention in newly diagnosed RA. There is little or no controversy among rheumatologists regarding the importance of early intervention. However, the referral of patients to a rheumatologist is often delayed many months for several reasons (patient-related factors, general practitioner hesitation, and waiting lists). Therefore, although the establishment of "early arthritis" clinics has been beneficial, it has proven difficult to implement this important aspect of treatment into common clinical practice.

Initial mono- or combination treatment with DMARDs

Several trials have investigated whether initial combination therapy in early RA is superior to monotherapy, and the issue is still under debate.

Some classical trials of mono- versus combination therapy in early RA such as the COBRA (26) and the FinRACo (27) studies showed that sulphasalazine (SSZ) as monotherapy was inferior to sulphasalazine in combination with other conventional drugs (DMARDs). Sulphasalazine as monotherapy is now used less frequently (except in women with a pregnancy wish in which case the use of MTX is contraindicated), and MTX has become the drug of first choice in the treatment of RA. A clinically more relevant question is therefore whether MTX in combination with other DMARDs is superior to MTX given alone as first line therapy. The answer remains open, because studies that compare MTX as monotherapy to therapy combinations of MTX with other DMARDs are scarce. Many of them do not reflect modern treatment strategy, either because the MTX dosage is too low (5-10 mg per week) (136-140) or because they include obsolete drugs such as oral or parenteral gold (141).

The CIMESTRA trial aimed at remission with intra-articular glucocorticoids together with either MTX (up to 20 mg) in monotherapy or MTX combined with cyclosporine (2.5-4 mg/kg) (1-3). The major finding after 5 years was that 80 percent of patients had achieved 50% clinical improvement or more, and almost half of the patients had not progressed radiographically. The clinical response was higher in the combination therapy group after 1 and 2 years, but not after 5 years, and there was no difference in radiographic progression between the mono- and combination therapy groups. It is a strength of the study that the strategy with maximum inflammatory suppression was applied to both treatment arms. Thereby the isolated impact of combination treatment could be identified. The weaknesses of the study included the use of cyclosporine, which is very limited in today's treatment palette due to a fear of toxicity, although the low-dose regimen was well tolerated.

The MASCOt study reported that the combination of MTX and sulphasalazine was more effective than either drug alone in patients who had a sub-optimal response to sulphasalazine, but there was no difference in radiologic progression (142). One study investigated patients with an inadequate response to MTX and found – not surprisingly – that combination with leflunomide (143) was more efficacious than continuing MTX alone. These studies are not so relevant, since they are based on patients who had an inadequate response to the initial DMARD rather than on DMARD naive patients.

If the clinician decides on combination therapy, one question that arises is whether to combine MTX with sulphasalazine, hydroxychloroquine, or both. A double-blinded, randomised study

of DMARD naïve patients addressed this question (28). Triple therapy was demonstrated to be well tolerated and superior to the double combination of MTX and sulphasalazine or MTX and HCQ with regard to clinical efficacy (ACR20 and ACR50, but not ACR70). Despite the fact that this well-performed study did not include radiological outcomes, it is often cited as an argument for triple therapy as first line therapy in early RA.

The BeSt study captured some of the central questions regarding treatment strategy in early RA (76;78;144). The study was DAS-driven (i.e. treatment was intensified if a certain DAS goal was not achieved) and compared four different treatment strategies given head-to-head in an open-label, randomized design: 1) Sequential monotherapy with MTX (7.5-30mg weekly); 2) step-up combination therapy (MTX initially, the addition of sulphasalazine 2 g/day and thereafter hydroxychloroquine 200mg/day); 3) initial combination therapy (MTX plus sulphasalazine) with prednisone (tapered from 60 to 7.5 mg daily) and 4) initial combination therapy with MTX plus infliximab (3mg/kg). Initial combination therapies (3 and 4) seemed to provide earlier clinical improvement, but all treatment strategies eventually showed similar clinical improvements after 4 years. Joint damage progression after 2 and 4 years was significantly lower in the two initial combination therapy groups compared with initial monotherapy, although the differences were small. A major weakness of this study is the open design, which may have biased the clinical response rates and the incentive in patient and physician to change treatment. Furthermore, the design does not allow us to identify whether the improved response in group 3 should be attributed to sulphasalazine and hydroxychloroquine or to high dose prednisolone. Scatter plots of radiographic change after 2 years reveal that the poorer outcome in the monotherapy group was driven by a number of patients with high baseline joint damage. The combination groups had been assigned fewer patients with high baseline scores.

A meta-analysis of efficacy and toxicity of combining DMARDs in RA concluded that in DMARD naïve patients the balance of efficacy/toxicity favours MTX monotherapy, and that in patients with inadequate DMARD response the evidence was inconclusive (145).

In conclusion, the issue of initial combination therapy of DMARDs or not in early RA has not been settled. Combination of MTX with other DMARDs may increase the clinical efficacy, but there are no convincing data that combination treatment is superior when it comes to the prevention of radiographic damage.

Tight disease control or routine care with DMARDs

It has been suggested that the trials that achieve the best clinical and radiographic results are not those, which merely compare agents, but rather those which aim at remission and maintenance of tight disease control and allow discretion of the physician to adjust therapy according to quantitative findings of inadequate response during the trial (146).

The strategy of tight disease control was first and most thoroughly investigated in the TICORA study (75). It was hypothesized that improved outcome could be achieved by employing a strategy of intensive outpatient management of patients with RA of less than 5 years duration treated with conventional DMARD therapy. Patients were randomized to either an intensive management or routine care group. Intensive management involved monthly visits with calculation of DAS score, injection of any swollen joint and adherence to a standard treatment protocol. Treatment was escalated every month after the first 3 months if

DAS score was > 2.4. The routine care group were seen in the clinic every 3 months, treated according to the physician's decision and DAS score was not systematically assessed. The odds for achieving a good response after 18 months were 5.8 in favour of the intensive group, and radiographic progression was reduced by nearly 50%. Sixty-five % were in remission in contrast to 16% in the routine care group. The study gave support to the hypothesis that tight disease control can be achieved in most early RA patients with a strategy of intensive treatment, and that this may be done with conventional DMARDs without the use of anti-tumour necrosis factor treatment. The study design had some weaknesses: It was unblinded, and the intensive group was treated by the principal investigator whereas the routine care group was treated by other physicians.

The CAMERA study aimed at tight disease control with frequent visits (monthly) at the clinic, and rapid dose escalation of methotrexate (from 7.5 to 30 mg weekly in 18 weeks) tailored to the individual patient on the basis of predefined response criteria, using a computerised decision-making algorithm. This strategy was compared with a group who received standard care (3-monthly visits) with methotrexate (from 7.5 to 30 mg in 52 weeks) (77). The main finding was that after 2 years, 50% of the intensive strategy group had been in remission for at least 3 months, in contrast to 37% in the conventionally treated group. However, it should be noted that the effect was most pronounced in the first months after inclusion, and after 2 years, the clinical and functional changes from baseline were similar between the two groups. In both groups, approx. 50% did not progress radiographically.

In the CIMESTRA study, treatment with DMARDs and intra-articular glucocorticoids was individualized, aiming at tight inflammatory control. After 5 years, almost 80% of the patients were in remission, and half of the patients had not progressed radiographically since baseline (3).

Thus, there is evidence that the goal of disease control can be achieved with MTX as the anchor drug in a much larger proportion of patients than previously thought. Frequent visits (monthly) allow frequent dose adjustments, and partial responders to MTX (who should be considered for other treatments) are identified earlier.

Oral or parenteral methotrexate

There is consensus that MTX should be given in adequate doses, i.e. 15 mg weekly or more to obtain the best effect, and folic acid supplementation of e.g. 5-15 mg weekly is generally recommended to prevent adverse events. Oral administration is first choice, whereas the role of parenteral (subcutaneous or intramuscular) administration has not been agreed upon.

In clinical practice, oral administration of MTX is frequently used in the initial phase, while parenteral MTX is considered in cases with lack of efficacy or adverse events. Pharmacokinetic studies comparing the oral and parenteral routes of administration suggest that the latter may be efficacious in patients failing oral MTX. Thus, when administered in doses greater than 7.5 mg/week, intramuscular MTX offers a higher bioavailability than oral MTX because of higher serum concentrations and a more prolonged exposure to the drug (147;148). However, studies concerning the efficacy and adverse events of parenteral MTX in clinical practice are few, small, and of short duration (149-153). In a retrospective study of 212 patients (154), the main reasons for switching from oral MTX to parenteral MTX were lack of efficacy (66%) and adverse events (28%). After 6 months, 54% of the

patients were still receiving intramuscular MTX therapy, and their median serum C-reactive protein and the use of glucocorticoids had decreased. Survival analysis revealed a median adherence to intramuscular MTX therapy of 6 to 8 months. This suggests that the benefit of parenteral MTX therapy was most often only temporary, although one in five continued parenteral therapy for more than 24 months.

One study compared the clinical efficacy and tolerance of MTX in patients with RA who were switched from intramuscular to oral administration because of a shortage of the intramuscular preparation (153). When MTX was first switched from intramuscular to oral administration, increased disease activity, exacerbation of morning pain and hand stiffness, duration of morning stiffness, increased joint pain, and increased joint swelling were observed. There were more gastrointestinal symptoms, but no increase in liver abnormalities. When intramuscular MTX became available again, one third of the 143 patients were switched back with subsequent improved disease manifestations and reduced side effects.

In conclusion, parenteral MTX may be considered in RA patients who have adverse events or lack of efficacy from oral treatment in adequate dosages.

How should glucocorticoids be used?

The role of glucocorticoids in the treatment of RA remains an area of dispute. The euphoria that glucocorticoids first caused, when their dramatic effect on disease activity in RA patients was discovered, was followed by rational – and irrational – fears caused by the severe adverse events that occurred during high-dose use. Since the 1980s, low dose glucocorticoids in doses of 10 mg/day (preferably 5 mg/day or less) have regained some of their good reputation; both as bridging therapy initially in the disease course and as an important supplement in periods with disease exacerbation (35;155). Low dose glucocorticoids rapidly relieve signs and symptoms of RA, but they also reduce joint destruction (35;82;156).

Theoretically, intra-articular administration has the advantages over systemic treatment of ensuring a high concentration of glucocorticoids at the site of inflammation, and it has been used successfully in studies of early RA (1;36;75;82). Despite this, many rheumatologists are reluctant to inject small joints and prefer to prescribe systemic treatment. To our knowledge, only one RCT has compared multiple joint injections of glucocorticoids with systemic administration (157). Four weeks after unguided, intra-articular injections, 44% of the patients had achieved an ACR50 response, compared to 20% of the patients who received systemic (intra-muscular) treatment with the same dose. In addition, the number of side effects was lower in the intra-articular group.

Based on a study from 1993, which demonstrated that half of the wrist blind injections were considered to be extra-articular, it has been argued that injection into small joints must be ultrasound guided to ensure accurate deposition (158). A randomized double-blind study, however, concluded that US did not increase the accuracy of wrist injections, when they were performed by an experienced rheumatologist, and no statistical significant differences in clinical responses were found during 12 weeks' follow-up between the ultrasound guided and the blind intra-articular injections (159). A recent randomized double-blind study of 184 patients also concluded that there was no significant difference in clinical outcome between ultrasound guided and unguided injections (160).

During the first 2 years of the CIMESTRA study, 1579 joints were injected unguided with betamethasone. The effect lasted 96 weeks (median time before relapse of synovitis) in proximal interphalangeal (PIP) and MCP joints, for other joint groups the effect durations were: shoulders 88 weeks; knees 68 weeks; elbows, wrists and ankles: 36-42 weeks. Seventy-five percent of the PIP joints and 64% of the MCP joints injected once and 64% of MCP joints injected twice stayed in remission (161). The injections had a rapid onset of anti-inflammatory action, the cumulative dose was moderate and no adverse events related to the intra-articular route of administration were reported (1-3).

In conclusion, treatment with oral low-dose glucocorticoids has a beneficial effect in RA, and intra-articular injections of glucocorticoids may be an effective, well-tolerated alternative to systemic treatment in a strategy aiming at inflammatory suppression.

Are all TNF α blockers equally effective?

In RA patients with an insufficient response to DMARD treatment (including MTX therapy in adequate dosages) initiation of treatment with a TNF α blocker should be considered. Guidelines for prescription of biological drugs as well as which drug to choose as first choice vary according to e.g. reimbursement rules and local or national recommendations. The TNF α blockers adalimumab, etanercept and infliximab have shown impressive clinical and radiographic efficacy in comparison to placebo in a number of large, well-conducted RCTs of MTX resistant patients (104;106;107). The drugs are preferentially used in combination with MTX, which improves treatment efficacy, leading to nearly arrest of progression in joint destructions at the group level.

Since the trials typically have very strict inclusion criteria, the generalizability of the trials has been questioned. The typical RA patient treated in routine care often has lower disease activity, higher age, more comorbidities and co-medications than patients in RCTs. Longitudinal observational cohorts or registries have complemented the RCT with data on real-life patients treated in routine care. In the RCTs of MTX resistant patients, an ACR50 response was reported in 21 to 69% of patients after one year (104;106;107). Data from the German RABBIT register showed that for infliximab-treated patients, ACR50 was achieved in 27% after 6 months, for etanercept-treated patients it was 37%, and for adalimumab-treated patients it was 39% (110). This was among the patients that would have been eligible for RCT participations, with lower numbers in ineligible patients. The Dutch DREAM register did not present ACR50 responses, but ACR20 responses were consistently lower than reported in RCTs, unless they only included the patients that would have been candidates for RCT participation (111). Data from Sweden and Denmark do not support those findings. Swedish data reported 32-44% to fulfil the ACR50 responses after 12 months (66), and data from DANBIO showed ACR50 to be achieved in 43% of patients (6), indicating a clinical response in routine care matching that obtained in RCTs. The reasons for these discrepancies between registries are not known, but may arise from inherent differences between the study cohorts regarding disease characteristics, treatment criteria, and various biases. The finding stresses the importance of publication of data from different registers and cohorts that each represents unique patient populations.

Few attempts have been done to compare the efficacy of the different TNF α blockers. No RCTs on this important issue have been published. Two meta-analyses of RCTs of MTX resistant RA

patients published 3 and 6 years after marketing, respectively, were not able to show any differences in efficacy (108;116), although RR estimates in the former suggested that etanercept might be more efficacious than both infliximab and adalimumab. A third meta-analysis from 2008 concluded that all TNF α blockers were not different from each other (117). However, all studies suffered from lack of statistical power with wide CI. A Cochrane review reviewed all previous Cochrane reviews on RCTs of biological agents and presented an indirect comparison based on the RCT data of a total of 4293 patients (including placebo-treated patients) (119). Although the ratio RR estimates suggested adalimumab and etanercept to be more efficacious than infliximab, the indirect comparison estimates were not able to show differences in efficacy (Ratio RR for achieving an ACR50 response) between the TNF α blockers: Adalimumab vs. etanercept: 1.04 (0.65-1.66), p=0.868; adalimumab vs. infliximab: 1.42 (0.84-2.39), p=0.193; etanercept versus infliximab 1.36 (0.75-2.46), p=0.307. Also here, the CIs were wide. In terms of safety, adalimumab was more likely to lead to withdrawals due to adverse events compared to etanercept (OR 1.89 (1.18-3.04)), and etanercept was less likely to lead to withdrawals than infliximab (OR 0.37 (0.19-0.70)).

Since head-to-head comparisons of TNF α blockers will most likely never be carried out, data from observational cohorts of "real-life" patients have proved valuable. They allow direct comparison of the efficacy of the drugs in routine care. A study from the Dutch Dream registry reported larger DAS28 improvements for adalimumab patients and etanercept patients than for infliximab patients (120). Drug retention rates, which may be considered a surrogate marker for efficacy, also varied between drugs, with discontinuation of treatment being significantly higher for infliximab patients compared to adalimumab patients and etanercept patients (120). A study from the South-Swedish SSATG registry compared infliximab and etanercept and reported higher ACR20 response rates at 6 months for etanercept patients compared to infliximab patients (61% and 47% of patients, respectively). Adherence to therapy was better for etanercept than for infliximab (one year drug survival approximately 85% vs. 60%) (66). Data from the DANBIO registry showed that the OR for an ACR70 response after correction for various confounders was 2.1 for adalimumab versus infliximab, 1.8 for etanercept vs. infliximab and not significantly different between adalimumab and etanercept (7).

A recent Swiss study reported poorer drug survival for infliximab, mainly due to an increased risk of adverse events (121). They reported a drug survival of infliximab-treated patients to have a half-life of approximately 2 years. DANBIO data found that etanercept had the longest drug survival, adalimumab intermediate and infliximab the shortest drug survival regardless of the reason for withdrawal (7). A French study of 304 RA patients support this finding (122).

In the interpretation of these results, the non-randomized, open design of an observational registry with its clear limitations and inherent biases should be kept in mind.

Infliximab, adalimumab and etanercept have in RCTs demonstrated a convincing ability to halt joint destructions at a group level, when they are given in combination with MTX. Annual progression rates of -0.7 to 1.6 units were reported, in contrast to 2.8 to 7.0 units in the MTX-treated controls (104;106;107). Since RA patients in RCTs are selected to have high disease activity with many tender and swollen joints, elevated acute phase reactants etc, the results are not easily generalizable.

Studies of observational cohorts may complement the RCTs and investigate whether the radiologic benefits of treatment with biological agents can be extended to patients treated in routine care. It is particularly important since it is well known that real-life patients often pause treatment for weeks or months due to inter-current events e.g. surgery and infections.

To our knowledge, only three studies have been published that investigated this issue in routine-care patients. Data from the Swiss registry on 372 patients treated with TNF α blockers for at least 10 months showed that during 1.5 years of follow-up, etanercept and infliximab appeared to offer similar protection against progressive structural joint damage and most effectively when given in combination with MTX (162). Different scoring methods (the Ratingen score and Joint Space Width, the latter is a computer-based method) hinder direct comparison with the results of the RCTs.

The Czech National Registry published a study of 99 patients, who had failed at least two DMARDs, had DAS28 > 5.1 at baseline and were treated with infliximab for one year. The observed radiographic progression (assessed by modified TSS of hands and feet) was compared with the projected, estimated rate (calculated on disease duration) and radiographic progression was reported to be 4.2 times slower than estimated (163). Two thirds of patients did not progress radiographically during the study.

In a DANBIO project, x-rays of hands and wrists were collected approximately 2 years before the onset of TNF α blocker treatment, at the time of treatment start and 2 years after initiation. Preliminary data on 157 patients showed that during treatment with TNF α blocker, the mean radiographic progression rate was 1.2 units/year, which was a 65% reduction compared to the progression rate during the period on conventional DMARD treatment (2.7 units/year). A total of 45% of patients progressed radiographically during 2 years of TNF α blocker treatment vs. 68% during DMARD treatment (60).

Considering that halting of radiographic progression is a very important goal in today's treatment of RA, more observational studies are needed on this issue to throw light upon a number of unknown issues: Is the impact of treatment irrespective of type of biological agent? What are the consequences of intermittent therapy? Which factors are associated with radiographic progression in routine care?

In conclusion, all TNF α blockers are efficacious in the treatment of patients with MTX-resistant RA both regarding clinical and radiographic disease control. However, significant differences in the clinical efficacy of and adherence to therapy of adalimumab, etanercept and infliximab have been observed in several European registries with the lowest treatment response and drug adherence rates reported for infliximab, whereas the relative performance of etanercept compared to adalimumab needs to be investigated further. Emerging data also indicate a beneficial effect of treatment with TNF α blockers on radiographic progression in patients with RA that are treated in routine care.

Biologics or DMARDs as first line therapy

The excellent data on TNF α blockers for the treatment of established rheumatoid arthritis soon prompted the pharmaceutical industry to set up studies of the use of TNF α blockers in early RA.

Three placebo-controlled RCTs have addressed the issue of use of TNF α blockers as first line therapy in early RA (infliximab, adalimumab and etanercept, respectively) (71-73). All 3

studies compared MTX in monotherapy with the TNF α blocker in combination with MTX in patients with early disease (max 2-3 years' disease duration). They were MTX naïve, had moderate-severely active RA with numerous tender and swollen joints and elevated acute phase reactants. In 2 of the studies, the patients were either IgM-RF positive or had radiographic erosions at baseline (71;72). All three studies reported significantly better clinical and radiographic outcomes for the combination therapy group than for the MTX monotherapy group. MTX was given in adequate dosages (escalating rapidly to 20 mg/week) with folate supplementation. TNF α blockers were given in standard dosages except in (72) that allowed dosage increase after week 16 in non responders. It is important to notice that the outcomes for the MTX monotherapy groups were highly satisfactory in many patients. The authors acknowledge that the results may not be generalizable to the population of early RA patients, who have less severe RA.

In the BeSt study, at four years follow-up (144), the group that received infliximab initially (in combination with high dose MTX) did not perform better clinically or radiographically than the group that received initial combination therapy with MTX, sulphasalazine and prednisolone. In a post-hoc analysis of the BeSt study, the authors compared the patients who received MTX and infliximab as initial treatment with those who started it after failing traditional DMARDs (164). They found more HAQ improvement and less progression of joint damage in the former group. However, here it should be kept in mind that the latter group are DMARD non-responders and therefore likely to have more severe disease.

In conclusion, the relative benefit of biologic combinations over conventional DMARD and glucocorticoid combinations in early RA remains uncertain. Further studies are needed to determine which subsets of patients that may benefit from first-line TNF α blocker therapy, to avoid over-treating the patients who have a milder disease. First-line TNF α blocker treatment should in any case be given in combination with MTX. The substantial investments in the trials by the pharmaceutical companies should also be taken into account in the judgment of definite evidence of greater benefit (132).

PREDICTORS OF DISEASE ACTIVITY AND DISEASE COURSE – ON THE ROAD TO PERSONALIZED MEDICINE

In the search for predictors – whether this encompasses radiographic progression or clinical non-response – it is important to keep in mind that the identified predictors depend on the patient material on which they were developed. Thus, predictors that were highly significant during a period in which the pyramid strategy was applied may not be equally relevant in cohorts of patients treated according to today's stricter treatment goals.

Study design may influence the range of potential predictors that are investigated in a certain project. In a RCT with substantial economic and personnel resources allocated, various spin-off projects may be launched, including studies of experimental, laboratory, imaging and other potential predictors. This is rarely possible to carry out in an observational study with limited resources allocated to collecting additional blood samples or making expensive additional investigations. Thus, in the CIMESTRA project, a large panel of potential predictors of radiographic progression was investigated, including environmental, genetic and imaging studies. In the DANBIO, the search for predictors was limited to correlations between various baseline vari-

ables and clinical responses. Below, the findings from these studies are discussed in context of the current literature.

Modern treatment strategies aim at inflammatory control immediately after diagnosis to prevent joint destruction (1;70;75;78). However, despite an aggressive strategy in the treatment of early RA, 25 to 50% of patients progress radiographically within 1 year of diagnosis (1;51).

Substantial efforts have been exerted to identify the subset of patients with poor prognosis for radiographic progression at the time of diagnosis and several promising prognostic markers have been identified. Traditionally, high disease activity as well as radiographic erosions and IgM-RF positivity at disease onset have been associated with poor prognosis (165), but these variables cannot predict radiographic progression in individual patients. Newer prognostic markers such as anti-CCP antibodies and MRI have shown promising results. A meta-analysis concluded that the presence of anti-CCP antibodies in patients with RA was associated with greater radiographic progression, and that the risk of radiographic progression was greater for patients with anti-CCP antibody positivity than for those with IgM-RF positivity (53). A number of MRI studies have shown bone marrow oedema at disease onset to be related to the progression of joint damage 1-6 years later (52;86;88), but these studies did not include anti-CCP. A recent study that included MRI and anti-CCP in the model and had 1 year of follow-up, found that bone marrow oedema and male gender were independent risk factors for radiographic progression (89). The CIMESTRA prediction studies showed that anti-CCP antibodies, MRI bone marrow oedema and baseline Sharp score were independent predictors of radiographic progression after 5 years (3).

Few observational studies regarding predictors of radiographic progression have been published. In a Danish study of 283 biologically naïve patients with RA, who started treatment with a TNF α blocker, preliminary results showed that high age and presence of IgM-RF were predictors of radiographic progression 2 years later, whereas other potential variables such as age, gender, disease duration, concomitant MTX and concomitant prednisolone were not predictive (61).

Although TNF α blockers have dramatically improved the treatment for RA, a substantial proportion of patients do not respond to them. Since TNF α blockers are very costly and have a potential for serious toxicity, it would be of significance if the use of these drugs could be targeted at the patients who will respond well. A number of studies from observational registries have tried to identify clinical variables as potential predictors of treatment response.

A study of 2879 British patients with RA found a higher baseline HAQ score to be correlated to a lower EULAR good response rate, while a better response was associated with current use of NSAIDs (suggested by the authors to be a surrogate marker for absence of comorbidities). Concomitant MTX was only significant in the etanercept-treated patients (55). In 1565 Swedish patients, concomitant MTX and low HAQ were both associated with good treatment response (56). Data from the DANBIO registry identified older age, low functional status and concomitant prednisolone as negative predictors of an ACR70 response, whereas concomitant MTX was only associated with EULAR good response (7).

Low functional status (as judged by a high HAQ) was thus the only clinical baseline parameter that was identified in all 3 studies. The studies do not allow any conclusions regarding causality due to their observational nature. One may speculate that

high HAQ reflects a higher degree of structural damage, which is not responsive to treatment. Another explanation may be that HAQ is associated with co-morbidities (166), which in themselves may be associated with reduced treatment response.

A new research area is to investigate which genetic factors that are involved in the response to TNF α blocker treatment. A number of single nucleotide polymorphisms (SNPs) that were associated with treatment response was identified by the use of genome-wide association scan (GWAS) technology in 89 patients with RA (167). It will be interesting to see if the results can be replicated in other publications.

In conclusion, promising potential predictors of radiographic progression have been identified, including anti-CCP. Some studies indicate that MRI might also be a useful supplement to the conventional examination programme in patients with early RA, in order to optimise the identification of patients at high risk of erosive progression. There is still a long way to go before it is possible to predict the treatment response in the individual patient. Clinical parameters may guide the clinician in groups of patients, but more sophisticated technologies are needed to identify correctly the patients that will benefit from a given treatment modality. The development in this field may lead to improved treatment strategies in the future.

CONCLUSIONS

The aims of the studies were to evaluate the effects of modern treatment strategies on disease activity and disease course in patients with RA, and to identify predictors of response to therapy.

Two studies were set up and conducted: One RCT of patients with early RA that were treated aggressively with conventional DMARDs (the CIMESTR study) and followed up for 5 years, and one observational, national cohort study of RA patients with an insufficient response to conventional treatment that started treatment with TNF α blockers and were followed up in the DANBIO registry.

The main conclusions of the studies are:

1. An aggressive treatment strategy with MTX, placebo-cyclosporine/cyclosporine and intra-articular injections with betamethasone in patients with early RA aiming at control of inflammation right after diagnosis provided rapid, safe and sustained relief of signs and symptoms and halted radiographic progression in the CIMESTR study. Addition of cyclosporine to MTX during the first 2 years improved some – but not all – treatment responses up to 2 years, but did not at any time influence radiographic changes. At 5 years, remission had been achieved and no radiographic progression had been observed in the majority of patients.
2. Baseline MRI bone marrow oedema score of the wrist was an independent predictor of radiographic progression in hands, wrists and forefeet after 2 and 5 years of follow-up in the CIMESTR study. In addition, anti-CCP antibodies and baseline radiographic score (TSS) were independent predictors after 5 years.
3. Routine registration of adverse events observed in patients treated with etanercept or infliximab in the DANBIO registry during the first 2 years of post marketing clinical use picked up twice as many serious adverse events and 20 times as many adverse events as the spontaneous, mandatory reports to the Danish Medicines Agency.

4. Despite changes in prescription practice from year 2000 to 2005 (towards initiating TNF α blocker therapy in RA patients with lower baseline disease activity), DANBIO data showed significantly improved treatment responses during the same period.
5. Based on DANBIO data, older age, low functional status, and concomitant prednisolone treatment were negative predictors of a good treatment response and disease remission after 6 months in RA patients treated with adalimumab, etanercept and infliximab in clinical practice.
6. In TNF α blocker naive RA patients treated in routine clinical practice and registered in the DANBIO database, significant differences in the efficacy of and adherence to therapy with adalimumab, etanercept, and infliximab were observed. Infliximab had the lowest treatment responses, disease remission rates, and drug adherence rates. Adalimumab had the highest treatment responses and remission rates, whereas etanercept had the longest drug survival rates.

PERSPECTIVES AND FUTURE STUDIES

The shift in focus of treatment since the mid-1980's towards early and aggressive use of MTX and other DMARDs has improved the short- and long-term outcome for patients with RA. The marketing of TNF α blockers around year 2000 further revolutionized the treatment of this chronic disease, which is feared for its inflammatory symptoms and potential for joint destructions that may lead to work disability, reduced quality of life, and increased morbidity and mortality.

The present studies were conducted in order to add new knowledge to the ongoing efforts internationally to optimize the treatment of early RA, and to evaluate the impact of TNF α blockers in routine care of RA patients. This thesis has reported some aspects of the impact of modern treatment strategies on disease activity and disease course as well as investigated potential predictors. However, several important research questions remain to be addressed in future research projects. These include:

- To which degree can the beneficial results from the CIMESTR study be maintained after 10 years?
- What is the additional effect of TNF α blocker therapy to the CIMESTR strategy of early, aggressive inflammatory control?
- Is the CIMESTR strategy as good as treatment with TNF α blockers in early RA?
- To which degree do TNF α blockers prevent radiographical progression in clinical practice?
- What is the efficacy of the newer biological treatment modalities e.g. B-cell depletion (rituximab), T-lymphocyte co-stimulation blockade (abatacept), anti-IL-6 receptor blockade (tocilizumab) and the new TNF α blockers (cer-talizumab pegol and golimumab)?
- What is the best strategy when switching between different biological therapies is indicated?
- What is the long-term malignancy risk for the different biological agents?
- Can non-response be predicted by genetic techniques e.g. SNPs or microRNA? What is the significance of anti-drug antibodies?
- How do newer treatment strategies affect the risk of cardiovascular disease in patients with RA?

ABBREVIATIONS

ACR20	20% improvement according to The American College of Rheumatology criteria
AE	Adverse event
Anti-CCP	Antibodies against cyclic citrullinated peptide
AS	Ankylosing spondylitis
CI	Confidence interval
CIMESTRA	Cyclosporine, methotrexate and intraarticular steroid in early rheumatoid arthritis
CRP	C reactive protein
CSA	Cyclosporine A
DANBIO	The Danish Rheumatologic Database
DAS28	Disease Activity Score based on 28 joint count
DMA	Danish Medicines Agency
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
DTPA	Diethylene triamine pentaacetic acid
EDTA	Ethylene diamine tetraacetic acid
ELISA	Enzyme-linked immunosorbant assay
ES	Erosion score
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GC	Glucocorticoid
GWAS	Genome wide association scan
HAQ	Stanford Health Assessment Questionnaire
HCQ	Hydroxychloroquine
HLA	Human leucocyte antigen
HR	Hazard ratio
I.a.	Intra-articular
IRF	Institute for Rational Pharmacotherapy
IQR	Interquartile range
JSN	Joint space narrowing
MCP	Metacarpophalangeal joint
MRI	Magnetic resonance imaging
MTX	Methotrexate
OMERACT	Outcome Measures in Rheumatology
OR	Odds ratio
PIP	Proximal inter-phalangeal joint
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system
RF	Rheumatoid factor
RCT	Randomized clinical trial
RR	Relative risk
TSS	Total Sharp score
SAE	Serious adverse event
SD	Standard deviation
SE	Shared epitope
SJC	Swollen joint count
SNPs	Single nucleotide polymorphisms
TJC	Tender joint count
TNF α	Tumour necrosis factor alpha
VAS	Visual analogue scale

SUMMARY

The main aim of the thesis was to evaluate the impact of modern treatment strategies on disease activity and disease course in

patients with rheumatoid arthritis (RA), and to identify predictors for treatment response.

Two different treatment strategies were investigated: (A) Aggressive, conventional treatment aiming at achieving inflammatory control in patients with recent-onset RA and (B) Treatment with tumour necrosis factor alpha (TNF α) inhibitors in patients with RA, who had an incomplete response to conventional treatment. (A) was studied in a randomized, placebo-controlled clinical trial (CIMESTRA), whereas (B) was investigated in an observational, nationwide cohort study (the DANBIO database).

The main findings were:

1. Treatment strategy (A) with methotrexate (MTX) and injections of glucocorticoids into swollen joints had rapid and sustained effect and reduced disease activity and halted joint damage. Addition of cyclosporine during the first 2 years reduced disease activity for as long as it was given, but had no effect on the development of joint damage. After 5 years, the majority of the patients was in remission and had no progression of structural joint damage.
2. Bone marrow oedema by Magnetic resonance imaging (MRI) scans of the wrists predicted the development of structural joint damage 2 to 5 years later (based on x-rays). Anti-CCP antibodies and structural joint damage at the start of treatment were also independent predictors for joint damage after 5 years.
3. Routine registration of adverse events observed in patients who received treatment with etanercept or infliximab (TNF α inhibitors) in the DANBIO database picked up twice as many serious adverse events than the spontaneous, mandatory reports to the Danish Medicines Agency.
4. Despite changes in prescription practice for the treatment with TNF α inhibitors in clinical practice from year 2000 to year 2005 towards less stringent treatment criteria, DANBIO data showed an improved treatment response.
5. High age, low functional status and concomitant treatment with prednisolone were negative predictors of a EULAR good response and remission after 6 months of treatment with TNF α inhibitors in clinical practice.
6. In patients, who were naïve to treatment with TNF α inhibitors, significant differences between drugs were observed regarding treatment responses and adherence to therapies. Infliximab had the lowest treatment response, remission rates and adherence to therapy. Adalimumab had the highest treatment response and remission rates, whereas etanercept had the highest adherence.

In conclusion, the results from the CIMESTRA trial and the DANBIO database showed that an aggressive treatment strategy with conventional drugs and intra-articular injections with betamethasone effectively controlled disease activity and prevent structural joint damage in patients with early RA. TNF α inhibitors were efficacious in clinical practice in the treatment of RA patients that had failed conventional treatment. Differences between the TNF α inhibitors regarding efficacy and drug adherence were found. Predictors of disease course and treatment response were identified.

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