Efficacy, safety and cost-effectiveness of four TNF-alpha blocking agents for the treatment of ankylosing spondylitis

Review on TNF-alpha blocking agents in ankylosis spondylitis for ZonMw

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory condition that primarily affects the spine and sacroiliac joints, causing pain and stiffness. Chronic spinal inflammation (spondylitis) can lead to fusion of the spinal vertebrae (ankylosis), which is debilitating and irreversible. The disease is not only limited to the spine; many AS patients also suffer from periodic inflammation of peripheral joints (particularly of the hip and knee), as well as periodic eye inflammation (uveitis). The disease mostly starts in young adulthood, with a strong male predominance. The prevalence in the is 0.5-1%. (1)
AS belongs to the spondyloarthropathies, a spectrum of diseases linked through a genetic predisposition, which is conferred by the HLA-B27 antigen. Conventional management of AS involves regular physiotherapy and NSAIDs, together with DMARDs. Physiotherapy and exercise are recommended as first-line therapies. Second line therapies include DMARDs such as sulfasalazine (SSZ), however, the efficacy is sometimes doubted and probably less than in rheumatoid arthritis. In recent years TNF-alpha blocking therapy appeared to be a new option for the treatment of AS.(2)
A drawback of TNF-alpha blocking therapy are the high costs. The yearly costs of therapy with TNF-alpha blocking agents areapproximately €15.000 per patient and it is subject to debate whether these costs outweigh the benefits of therapy. It is important to realize that these benefits not only consist of clinical efficacy but also of improved quality of life, reduced work absenteeism, and perhaps less orthopaedic surgery. The gain of reducing work absenteeism is especially important in patients with AS since the onset of disease in these patients is at a much younger age than other inflammatory rheumatic diseases. Furthermore, TNF-alpha blocking agents probably also have favourable effects on common co-morbidities observed in patients with inflammatory rheumatic diseases, particularly osteoporosis, cardiovascular disease and uveitis. With respect to the increasing costs in healthcare it is important to critically evaluate the necessity of certain expensive therapies.
In this review we summarized the evidence from the literature with respect to the major efficacy, safety and cost-effectiveness data on the four TNF-alpha blocking agents, that are currently registered in the Netherlands. In addition, existing guidelines and protocols with respect to treatment of AS with TNF-alpha blocking agents are discussed. Where available, a selection of data from clinical registries in the Netherlands and other European countries will be given, in which long term follow up of therapy with TNF-alpha blocking agents in patients with AS is performed. Long term efficacy and safety data will also be addressed. In another paragraph the expenses of medication in the Netherlands are discussed and compared to other Western European countries. There are still several unresolved issues with respect to therapy with TNF-alpha blocking agents in patients with AS. Therefore in the final paragraph, we will mention some topics where research is ongoing related to therapy with TNF-alpha blocking agents in patients with AS.

1) Summary and place in the clinical armamentarium

In rheumatology biologicals that inhibit TNF are widely used since their introduction in the '90s. (table 1) (3). The four registered agents that were studied were adalimumab (Humira®), etanercept (Enbrel®), infliximab (Remicade®) and golimumab (Simponi®).

All four registered TNF-alpha blockers are effective in patients with active AS, who have had inadequate responses to NSAIDs and/or sulfasalazine in case of peripheral arthritis. TNF-alpha blocking agents are mostly prescribed as monotherapy. An important reason for secondary non-response appears to be antibody formation to the drugs, the so-called immunogenicity. The major adverse events are infections, which occur at an increased rate and can partly be managed by screening and pretreatment of latent tuberculosis. Quality of life improvements after anti-TNF therapy in AS are impressive and probably larger than in patients with rheumatoid arthritis. (4)

The societal costs of inadequately controlled AS justify intensive treatment and probably also expensive therapy. Presently, there are not enough data to conclude whether TNF-alpha blockers are effective in maintaining or regaining employment in patients with AS. Future areas of research should include, among others,: profiling of patients to better predict the response to TNF blockers ("personalized medicine"), the effect on cardiovascular risk, evaluating withdrawal of these drugs during sustained remission and the response to other biologicals, preferably relative to the response to TNF blockade and lowering immunogenicity by concomitantly prescribing methotrexate or other immunomodulators.

Table 1. Indications for TNF inhibitors (source: FDA)

TNF inhibitor:	Indication:
adalimumab (Humira®)	AS, PsA, RA, JIA, CD, psoriasis
infliximab (Remicade®)	AS, PsA, RA, UC, CD, psoriasis
etanercept (Enbrel®)	AS, PsA, RA, JIA, psoriasis
golimumab (Simponi®)	AS, PsA, RA
certolizumab pegol (Cimzia®)	CD, RA

AS: ankylosing spondylitis, PsA: psoriatic arthritis, RA: rheumatoid arthritis, JIA: juvenile idiopathic arthritis, CD: Crohn's disease, UC: ulcerative colitis

2) Pharmacotherapeutic value

Methods

Search strategy

A search was performed by an experienced librarian using the Cochrane database, MEDLINE and OVID databases. For the search, the following terms were used: "Spondylitis, Ankylosing"[Mesh] AND <TNF-alpha-blocking-agent-name> in the title (for search details see Appendix B). The search was limited to systematic reviews of randomized controlled trials (RCTs) in which one of the following TNF-alpha-blocking agents is compared to placebo or to another TNF-inhibitor: etanercept, adalimumab, infliximab, or golimumab. We also searched systematically for RCTs that had been published after the latest date that was used in the search strategy of the reviews included. Finally, we also searched for systematic reviews of economic evaluations and for additional economic evaluations published subsequently. If the selected reviews contained sufficient information on the outcomes we were interested in, no additional from the respective RCTs were included. If selected reviews contained duplicate data, we only included the review with the most complete report of the outcomes.

Box 1. Brief overview of search strategy to publications on efficacy and safety of TNF-alpha blocking agents in RA.

1. Ankylosing spondylitis AND infliximab OR remicade
2. Ankylosing spondylitis AND adalimumab OR humira
3. Ankylosing spondylitis AND etanercept OR enbrel
4. Ankylosing spondylitis AND golimumab OR simponi

Selection criteria

Selection criteria that were used:

- Systematic reviews (and RCTs and economic evaluations if published after inclusion date for studies in the review)
- Therapy with one of the four TNF-blocking agents
- Patients with objectively diagnosed AS
- Outcome measures include ASAS20, ASAS40, BASFI and BASDAI. (5)

Criteria for considering studies for inclusion

Recently published systematic reviews of RCTs, additional RCT's published after the publication date of the most recent review and economic evaluations were included. The included articles compared the use of adalimumab, etanercept, golimumab or infliximab (used at licensed therapeutic dosages) against placebo or other active treatments and reported on efficacy and/or safety outcomes.

Type of studies included

Participants

Studies that included adults of 18 years or older with definite AS (modified NY criteria), BASDAI ≥ 4, and a back pain score of ≥ 4 were considered.(6)

Type of intervention

Studies were included if TNF-alpha blocking agents were administered alone in standard, approved, doses or in combination with other biologic or traditional DMARDs compared to placebo alone or to placebo plus another biologic or traditional DMARD. For adalimumab, the subcutaneously administered, dose is 40 mg every other week. For etanercept the, subcutaneously administered, dose is 50 mg every week or 25 mg twice weekly. For infliximab the, intravenously administered, dose is 5.0 mg/kg body weight every 6 weeks after an induction scheme at week 0, 2 and 6. For golimumab the, subcutaneously administered, dose is 50 mg once a month.

Outcomes

Efficacy

The primary outcomes are the ASAS20 and ASAS40 at week 12 and week 24. The ASAS20 (40) is the percentage of patients with a 20% (40%) response according to the ASsessment in Ankylosing Spondylitis International working Group criteria for improvement and an improvement of at least 1 unit as compared with baseline in at least 3 of the following 4 domains with no deterioration (defined as a worsening of at least 20% or an absolute increase of at least 1 unit) in the remaining domain: patients global assessment of disease activity during the previous week (assessed with a 0-10 cm VAS) function represented by the Bath AS Disease Activity Index (BASDAI), a composite score of six questions on a 0-10 (or 0-100) scale. A score of 4 (or 40) or more is indicative of active disease, and Bath Ankylosing Spondylitis Functional Index (BASFI) score (assessed with a 0-10 cm VAS). (7;8). The BASFI and BASDAI scores are presented as reported in the original publications (0-10 or 0-100 scale)

Safety

Data on serious adverse events ((S)AE) (among others serious infections), withdrawal from the examined studies due to adverse events and deaths were extracted for the time points six months, twelve months and the end of follow-up.

Additional data that were collected were: type of participants, duration of disease, intervention and control therapy, dosage and frequency and duration of follow up.

Data-collection and data-analysis

Two reviewers (DJ and CvD) independently evaluated all titles and abstracts. Criteria for inclusion were: systematic reviews in which one or more of the TNF-blocking agents was compared to controls, objectively diagnosed AS according to the modified New York criteria, 18 years of age or older, and

inclusion of one of the primary outcomes ASAS20, ASAS40 or ASAS50. (9) Disagreements were resolved by discussion.

Results

The electronic database search resulted in 907 titles. From these 907 titles we excluded publications in which no patients with AS were included or in which none of the four TNF-blocking agents was used as treatment strategy. This first selection was based on the title and/or abstract. This resulted in 59 articles that were selected. From these 59 articles, 7 were systematic reviews and 23 were RCTs. Three of these seven systematic reviews, provided data on efficacy and safety as statedabove. The other four publications contained or no additional information or the authors did not systematically reviewed the literature.

Description of included reviews and RCTs

Two systematic reviews of RCTs that compared one or more of the TNF-alpha blocking agents with placebo were identified. Both were eligible for inclusion. (10;11) Of these one was a systematic review of RCTs in which adalimumab, etanercept or infliximab was compared to placebo and the other one included only one RCT in which golimumab was compared to placebo in patients with AS. However, the included systematic reviews also reported safety data, we also identified and included one systematic review of RCTs in which the incidence of serious infections was compared between TNF-alpha blocking agents and placebo in patients with AS. (12) This systematic review included 9 RCTs. Since the methodological value of indirect comparisons between TNF-alpha blocking agents are under debate, we only extracted data of the comparisons of the TNF-alpha blocking agents and placebo.

A serious infection was defined as: life-threatening, fatal, requiring intravenous antibiotics or hospitalisation or resulting in persistent or significant disability.

Adalimumab

For the comparison of adalimumab with standard treatment Mcleod et al included 2 placebo-controlled RCTs. In both studies patients with active AS were treated with adalimumab 40 mg once every 2 weeks. The duration of the trials was 24 weeks. The mean BASDAI at baseline was 6.3 for the treatment group and 6.3 for the controls. The mean BASFI was 52.4 for the treatment group and 56.4for the controls.

Efficacy of adalimumab

Mcleod et al reported a pooled RR for the ASAS20-score at 12 weeks of 2.43 (95%CI: 1.76-3.35), in favor of the adalimumab group. The RR for the ASAS50 at 12 weeks was 3.22 (95%CI: 1.98- 5.23).

Table 2. Characteristics of included RCT's in the review of Mcleod et al. on adalimumab and the BASDAI50 and the ASAS20 score at 12 and 24 weeks. (10)

Study	Treatment arms	Patient characteristics	Study duration	RR of ASAS20 at 12 wk (24 wk)	% achieved BASDAI50 at 12 wk (24 wk)
Van der Heijde, 2009 Maksymowych, 2010 (Canadian AS) (13)	Adalimumab 40 mg/ every 2 wks (n=38) Placebo (n=44)	Active AS	24 weeks (primary endpoint at 12 wks)	1.74 (-)	-
Van der Heijde (2006) (14)	Adalimumab 40 mg/ every 2 wks (n=208) Placebo (n=107)_	Active AS	24 weeks (primary endpoint at 12 wks)	2.83 (-)	2.19 (-)

Safety of adalimumab

The review of Fouque-Aubert et al. included one RCT in which the incidence of serious infections in patients with AS treated with adalimumab was compared to placebo. (14) In this study 208 adalimumab patients and 107 controls were compared. No patient in the treatment group and one patient in the control group had a serious infection during 24 weeks of follow-up. The data was to limited to draw conclusions regarding serious adverse events.

From two studies, Van der Heide 2005 (Atlas) and Van der Heide et al. 2009 (Maksymowich) Canadian AS) data on safety were available. (13;15) In one study, adverse events were only specifiedin serious and not-serious adverse events. Serious adverse events occurred in the adalimumab group (n=246) in 2% of the patients at 12 weeks and in 2.8% of the patients at 24 weeks, compared to 1.3 and 2% in the placebo group (n=151) respectively.

Etanercept

For the comparison of etanercept with standard treatment Mcleod et al included five RCTs which all were suitable for our present report. (16-20) All five studies included patients with active AS. The duration of the trials ranged from six weeks to four months. Etanercept was administered in a dose of 25 mg, twice a week. The BASDAI at baseline ranged from 3.0 to 6,5 for the treatment group and from 3.0 to 6.6 in the placebo group.

Table 3. Characteristics of included RCT's in the Cochrane review Mcleod et al. on etanercept and ASAS20 response for the treatment arms. (10)

Study	Treatment arms (numbers ptns)	Patient characteristics	Study duration	RR of ASAS20 (95% CI) at (x) wks	% achieved BASDAI50 (weeks)
Brandt (2003) (16)	Etanercept, 2/wk (16) Placebo (17)	Active AS	6 weeks (observational afterwards)	3,5 at 6 wks	57 (6) 6 (6)
Calin (2004) (17)	Etanercept, 2/wk (45) Placebo (39)	Active AS	12 weeks	2.50 (1.34-4.68) at 12 wks	……
Davis (2003) (18)	Etanercept, 2/wk (138) Placebo (139)	Active AS	24 weeks	2.12 (1.57-2.86) at 12 wks 2,6 at 24 wks	……
Gorman (2002) (19)	Etanercept, 2/wk (20) Placebo (20)	Active AS	16 weeks	2.67 (1.32-5.39) at 16 wks	……

Efficacy of etanercept

The data of the four RCT's with available ASAS20 responses at several timepoints are presented in table 3. In none of the studies the 95% confidence interval of the RR for ASAS20 (at several endpoints) exceeded zero, indicating that etanercept results in statistically significant improvement of the ASAS20. (table 3)

Safety of etanercept

In the aforementioned review of Fouque-Aubert et al. five RCTs were included in which the incidence of serious infections in patients with AS treated with etanercept was compared to placebo. (16-19;21). A serious infection was commonly defined as life-threatening, fatal, requiring intravenous antibiotics or hospitalisation or resulting in persistent or significant disability. These serious infections were not further specified. The duration of follow up in these 5 RCTs ranged from 12 – 30 months, of which the two largest RCTs had a duration of 12 and 24 weeks in which 312 and 246 patients, respectively, completed follow up. The pooled data showed a total of four serious infections in 524 patients treated with etanercept and one infection in 266 patients in the placebo group, indicating a doubled risk for serious infection in the etanercept group, however, this difference did not reach statistical significance. Also non-serious infections were recorded, however, these were not further specified. The pooled incidence for non serious infections was 20% in the placebo group and 23% in the treatment group.

Infliximab

For the comparison of infliximab with standard treatment Mcleod et al included 2 RCTs with a total of 235 patients in the treatment group and 113 patients in the control group. (22;23) In both studies patients with active AS were treated with infliximab 5 mg/kg. The duration of the trials was 24 and 12 weeks. The mean BASDAI at baseline was 6,5 and 6.6 for the treatment group and 6.5 and 6.3 for the placebo group. The mean BASFI at baseline was 5.7 and 5.4 for the treatment group and 5.1 and 6.5 for the placebo group.

Table 4. Characteristics of included RCT's in the Cochrane review Mcleod et al. on infliximab and ASAS20 response for the treatment arms. (10)

Study	Treatment arms	Patient characteristics	Study duration	RR of ASAS20 at 24 weeks	% achieved BASDAI50 (weeks)
Van der Heijde (2005) (ASSERT) (23)	Infliximab 5mg/kg i.v. (n=201) Placebo i.v. (n=78)	Active AS	24 weeks	5.43 (24 wks)	51 (24) 10,7 (24)
Braun, (2002) (22)	Infliximab 5mg/kg i.v. (n=35) Placebo (n=35)	Active AS	12 weeks	2.37 (12 wks)	53 (12) 9 (12)

Efficacy of infliximab

Mcleod et al reported a pooled RR from the two studies for the ASAS20-score at 12 weeks of 4.11 (95%CI: 2.62-6.44), in favor of treatment group. The RR for the ASAS20 at 24 weeks was 2.80 (95%CI: 2.11- 3.71), which was based on only the study of Van der Heijde et al. (23)

Safety of infliximab

Of the 202 patients treated with infliximab in the ASSERT study, 166 (82%) experienced any AE compared with 54 (72%) of the 75 participants in the placebo group. SAEs were reported for seven (3.5%) of the infliximab-treated individuals and two (2.7%) of the placebo group. Braun et al reported that three patients (8.8%) experienced serious AEs resulting in withdrawal from the study. None of the placebo group experienced such serious AEs or withdrew. Of the three patients experiencing serious AEs one person developed TB, one allergic granulomatosis of the lung and the third transient leucopenia.

Golimumab

In a systematic review of Kay et al. only one study was included in which golimumab was compared to placebo in patients with AS. (11) This RCT with a duration of follow up of 24 weeks included patients who had active AS despite prior NSAIDs or DMARDs (24) Strategies that were compared were golimumab 50-mg every four weeks, golimumab 100-mg every four weeks and placebo every four weeks. The primary outcome measure of this trial was ASAS20 at 14 weeks. The BASDAI (0-10 scale) and the BASFI (0-10 scale) at baseline were 6.6 and 5.0 for the 50-mg group, 7.0 and 5.4 for the 100-mg group and 6.6 and 4.9 for the placebo group. The percentage of patients that were treated with concomitant MTX was comparable and about 20% in each treatment arm.

Efficacy of golimumab

The primary endpoint was the ASAS20 at 14 weeks. Of the patients who received golimumab, 59.4% in the 50-mg group and 60.0% in the 100-mg group achieved an ASAS20 response at week 14

compared with 21.8% in the placebo group, which differed significantly from each other. The ASAS20 response at week 24 was for all three groups similar compared with the score at week 14. At week 14 and week 24, patients who received golimumab showed statistically significant improvements in all components of the ASAS20.

Table 5. Characteristics of the RCT of Inman et al on golimumab in patients with AS and the respons on the ASAS20 in the treatment arms. (24)

Study	Treatment arms (n)	Patient characteristics BASDAI at baseline	Study duration	% change ASAS20 (week)	% achievesd BASDAI50 at 14 wk (24 wk)
Inman, 2008, (Go-Raise) (25)	Golimumab 50 mg/4 wks (n=138)	6.6	24 weeks (primary	59,4 (14)	45,9 (50,8)
	Golimumab 100 mg/4 wks (n=140)	7.0	endpoint at 14 wks)	60,0 (14)	40,9 (47,8)
	Placebo (n=78)	6,6		21,8 (14)	15,4 (14,7)

Safety of golimumab

Inman et al also report data with respect to adverse events during follow up. The percentage of serious adverse events in the three groups to which the patients were initially randomized was 6.5% in the placebo group, 3.6% in the golimumab 50-mg group and 6.4% in the golimumab 100-mg group. These numbers were not significantly different from each other. Malignancy occurred in one patient in the placebo group and one patient in the group of patients treated with 100-mg golimumab.

Summary on efficacy

The results presented above on the efficacy of the four TNF-alpha blocking agents that we evaluated by reviewing the available literature, show us that therapy with these agents is very effective compared to standard therapy (placebo including DMARDs) in patients with AS. The ASAS20 and ASAS40 outcomes of the individual studies significantly improved in patients treated with one of the TNF-alpha blocking agents compared to controls. Consequently pooled estimates of the data provide RR estimates that are precise and significantly different from 1.The efficacy of therapy seems to outweigh a potentially increased risk for adverse events.

Summary on safety

The data above do not indicate that there is an increased risk for SAEs in patients with AS treated with TNF-alpha blocking agents in comparison with placebo/usual care. However, it has to be realized that scarce but serious complications of therapy might not be observed in the relatively small groups of patients in RCTs and the relatively short duration of follow up. To gain precise insight in the risk for serious complications as malignancies or exotic infections long term follow up data to therapy with

TNF-alpha blocking agents has to be collected and analyzed. However, these cohort studies also have their limitations. In another paragraph of this review we will present and discuss these type of studies in more detail.

3) Clinical guidelines

According to the guideline Ankylosing Spondylitis of the Dutch Society for Rheumatology (NVR) and the ASAS guideline for the assessment of spondyloarthritis, (5;26) TNF blocking therapy is indicated if a patient diagnosed with AS meets the following conditions:

- Diagnosis based on modified New York. (6)
- Active disease during at least 4 weeks despite adequate treatment. Criteria for disease activity are a BASDAI-score of at least 4 and the expert opinion of the treating physician. "Adequate treatment" is defined as treatment with 2 NSAIDs in the highest tolerated dose for at least 3 months.
- In AS with axial disease no other additional treatment is necessary before anti-TNF treatment.
- AS patients with peripheral arthritis must be treated with 2 intra-articular injections with corticosteroids and 3 gram/day of sulfasalazine (SSZ), or the highest tolerated dose, for at least 4 months before starting anti-TNF treatment.
- An AS patient with enthesitis must be treated with 2 local injections of corticosteroids before initiating anti-TNF therapy.

If contra-indications are present or standard treatment options are not tolerated anti-TNF therapy can be initiated in a earlier stage. (27)

Among all DMARDs only SSZ 2000-3000mg/day is effective in the treatment of AS with peripheral arthritis. Low dose MTX is not effective in the treatment of AS, and adequate investigations with higher doses of MTX are lacking. Since TNF inhibitors are very effective in the treatment of AS and MTX is not part of usual care of AS, combination therapy with MTX is not recommended. However, this recommendation does not take into account the fact that MTX might help to lower the formation of anti-drug antibodies. A good clinical response, defined as relative BASDAI improvement of 50% or an absolute improvement of 2 points (BASDAI. Alternatively, an improvement of 20% of the ASAS criteria can be used with the drugs mentioned in this paragraph is achieved in 60% of the treated patients. (28)

Before starting anti-TNF therapy screening for the presence of latent or active tuberculosis and other contra-indications is obligatory. Therefore, the following surveys should be carried out:

- Active or latent infections, tuberculosis in particular (history; physical examination; chest X-ray; tuberculin skin test)

- Moderate to severe heart failure (NYHA class III-IV)
- History of malignancy
- History of demyelinating disease
- Planned pregnancy

Infections should be treated before the start of treatment, and if they occur during treatment, the TNF blocker should be temporarily discontinued. Vaccinations with dead vaccines e.g. influenza can be considered. In the case of elective high infection rate surgery, anti-TNF therapy should be stopped 4 times the half-life of the drug before and after the surgery. Before planned pregnancy the TNF-alpha blocking agents should be stopped at least 4 times the half-life of the drug. Breastfeeding during anti-TNF therapy is not recommended. Before starting treatment the patient should be informed about safety of anti-TNF therapy and what to do in case of side effects and emergency, and how to inject the drug. (29)

4 a and b) Daily clinical practice

Data from RCTs are valuable for investigating effectiveness of therapeutic interventions and safety outcomes that occur very often or shortly after initiation of therapy. However, there is also a risk for the development of less common, but also serious adverse events related to the intervention on the long term. The duration of RCTs is often too short to gain insight into these long term safety data. Therefore, data from cohort studies and registries in which data of several years of follow up are collected are useful.

In addition, responses observed in RCTs may be different from the response achieved in daily clinical practice as patients may differ in several aspects. (30) A clinical practice register is of value as it provides insight into the actual use of medication in daily practice, heterogeneity of the treated population and the related effectiveness and costs. In the sections below data are reported from European registries on important safety outcomes.

Safety data from registries

Long term safety (and to a lesser extent the long term effectiveness) of TNF-blocking therapy in daily clinical practice is probably not very different between the indications AS, PsA and RA. Several registries and databases have documented an increased risk of serious bacterial infections with the use of biologicals compared with patients not treated with these drugs. In particular, increased rates of pneumonia were seen, greatest within 6 months of treatment initiation, 2.9 versus 1.4 infections per 100 person-years (multivariable-adjusted HR 4.2, 95% CI 2.0-8.8). (27) A high HAQ score, older age, co morbidity and past hospitalisation predicted subsequent hospitalisation for infection. (27) A UK registry of 8,659 patients treated with TNF-blocking agents, demonstrated that there is a significantly increased risk for all serious infections during the first 90 days of therapy with biological agents compared with DMARDs (adjusted incidence rate ratio: 4.6; 95% CI 1.8-11.9). (28) No difference in infection rate between adalimumab, etanercept and infliximab was reported.

Other data from a Finnish registry (ROB-FIN) comprised a total of 229 patients with severe AS and who were followed for 24 months. After 24 months, 49 patients (21%) had discontinued their first biological drug, and 30 patients (13%) had been lost to follow-up. Twenty-five patients (11%) had experienced an AE while on therapy with of the first biological drug. AEs led to discontinuation of the first biological drug in 14 cases (6 %). (31)

In an analysis of 1440 patients with rheumatic diseases (61% RA, 26% SpA not further specified, and other diseases: 13%) registered in the ROB-FIN database, 917 were treated with a biological drug. In a 5-year period, 308 adverse events were reported in a total of 248 patients (17% of all patients in the ROB-FIN register). The most frequent adverse events were related to drug administration and consisted of local injection site and infusion reactions. These adverse events did not lead to any fatal

outcomes. Therapy with biologicals was stopped in about 50 percent of the patients in whom eczema or reactions at the injection site emerged. Infections comprised 28% (n=85) of the reported adverse events. The most commonly reported infections were sinusitis, upper respiratory tract infection, herpes zoster and urinary tract infection. (30)

Results from several international biological registries show an increase in the incidence of TBC infection in RA patients treated with TNF inhibitors compared to patients with RA not treated with TNF inhibitors and compared to the general population. (30-33) Tuberculosis risk has decreased drastically with the introduction of screening measures and prophylaxis for those with latent TBC infection before the start of anti-TNF therapy. (30;34)(3,7) When anti-TNF therapy was introduced for AS, tuberculosis prophylaxis was already practised as a consequence of the experiences in RA. Hence, only two cases of TBC, one pulmonary and one extrapulmonary, were reported in the Finnish registry. (30;34)

Malignancy

Although some cases of breast cancer and one case of acute myeloid leukaemia were reported no other malignancies such as lymphomas, were documented in the ROB-FIN registry. Data from several international biologicals registries and long-term, open-label extension data in patients – mainly with RA – receiving anti-TNF agents compared with the general population and with those taking traditional disease-modifying anti rheumatic drugs show that there is no overall increased risk of malignancy.(32-35) An increased occurrence of non-melanoma skin cancer, central nervous system tumours and colorectal cancer was suggested in a Swedish cohort, however, numbers were small and not statistically significant. (36) The pattern of malignancies in patients receiving anti-TNF therapy versus patients who are not treated with TNF inhibitors is comparable, except for non melanoma skin cancer, that occurs more frequent in patients treated with TNF-blocking agents. (36)

Employment status, work productivity and absenteeism

From the British society for Rheumatology Biologics Registry data on working status of 229 AS patients treated with anti-TNF therapy were reported. (37) Working status was reported at baseline and 3 years after inclusion and this was compared to biologic-naive rheumatoid arthritis patients. At baseline, work disability rate was 41% for AS patients and 36% for the control group. Working disabled AS patients were older (45 vs 42 years, p=0.020) had higher baseline HAQ (1.8 vs 1.2, p<0.001) and had a higher baseline BASDAI score (7.6 vs 6.6, p=0.001) compared to working AS patients. During 3 years of follow-up, 4% of patients became work disabled and 8.5% of the working disabled patients at baseline started to work again.

In a study with 19 anti-TNF treated AS patients (72% male, aged 29-64), 4 of 19 patients who were unable to work before the start with TNF inhibitors, returned to employment, and two others increased

their work-ability from part-time to full-time. Mean days lost from work due to sick leave decreased from 15 in the 12 months before treatment to 0.9 in 12 months after treatment initiation. (38)

In a RCT of 40 work unstable AS patients, improvement of the ankylosing spondylitis work instability scale (AS-WIS) was assessed during etanercept treatment or placebo for 12 weeks. At week 12 the AS-WIS was 2.75 in the etanercept group and 0.68 in the placebo group. However, this difference did not reach statistical significance. Risk of job loss decreased in 55% of etanercept treated patients vs 35% of the placebo group. Risk of job loss increased in 5% and 15% of etanercept and placebo group patients, respectively. (39)

In an open-label extension phase of a 24-week RCT with 315 adalimumab treated patients, adalimumab treatment was associated with sustained improvement in Work Productivity and Activity Impairment-Specific Health Problem Questionnaire (WPAI-SHP) scores. (40)

Infliximab treated AS patients in a RCT had more significant reduction in limitations of work and daily activity due to physical and emotional problems than patients treated with placebo. Of the patients working full-time, infliximab treated patients had a greater improvement in productivity after as early as 6 weeks compared to the placebo group. Also workday loss was reduced.(41)

5) Quality of life and physical functioning

In a North American study, therapy with etanercept in 149 patients with AS was compared to the general population and the total population of patients with chronic illness. At baseline AS patients had significantly lower (worse) scores of all 8 SF-36 scales compared to the general population. Compared to patients with other chronic illnesses, AS patients had the lowest scores in the physical domains of the SF-36, impairment in psychosocial components was less pronounced. Treatment with etanercept improved the health related quality of life in all 8 scales of the SF-36 compared to baseline, especially in the physical domains.(42)

A RCT with a duration of 12 weeks in which 356 patients with AS were included showed that patients treated with etanercept had significantly improved quality of life and functional status (measured with the BASDAI fatigue item, EuroQoL-5D utility, VAS and SF-36) compared to those receiving placebo. (43) In an open-label extension study, 257 AS patients were treated with etanercept for 72 weeks. 85% of these patients completed follow-up. Patients initially randomized to placebo had significantly lower values at SF-36, Euro-QoL and VAS compared to patients who were initially randomized to etanercept. At 12 weeks of the extension study this difference was not present anymore. Patients in whom etanercept treatment was continued had sustained health related quality of life improvements, and patients initially receiving placebo showed rapid and also sustained improvements after switching to etanercept treatment. (44)

Of 16 patients treated for 6 weeks with infliximab, 7 showed signs of depression and 4 of anxiety at baseline. These complaints diminished significantly after each infusion up to 6 weeks of treatment. Except for emotional role, all SF-36 scales improved in these patients during 6 weeks of follow up. These changes were not correlated to BASDAI, CRP or ESR levels.(45)

In a RCT in 356 AS patients treated with either golimumab or placebo sleep disturbance was assessed for 24 weeks using the Jenkins Sleep Evaluation Questionnaire (JSEQ). Patients with active disease had significantly more sleep disturbance at baseline, compared to patients with less active disease, due to underlying pain associated with AS. Treatment with golimumab reduced sleep disturbance and improved health related quality of life. (46). In a comparable study of patients treated with adalimumab during 12 weeks, overall sleep and sleep quality was improved by adalimumab treatment. (47)

6) Costs

Drugs account for somewhat less than 10% of total healthcare costs in the Netherlands. In figure 1 the pharmaceutical expenditures per person per year for several European countries are depicted. In 2008 in the Netherlands, € 335 per person was spent on medicines (including delivery of expensive drugs). The level of drug spending per resident did not change compared to 2007. In the surrounding countries on average the drug expenditure per resident is 18% to 68% higher than in the Netherlands (Belgium (€ 395), Germany (€ 458) and France (€ 564)). Due to increased use of expensive drugs, which in some countries are only available through the hospital, the costs of drugs in the Netherlands are increasing. The differences in drug consumption are partly explained by the differences in aging of the population in different countries. In the Netherlands, 15% of the population is 65 years and older. In France, Belgium and Germany, the proportion of residents of 65 years and older is 17%, 17% and 20% respectively. The use of drugs in patients of 65 years and older is a threefold compared to younger patients. In individuals 75 years and older the use of drugs is almost the fivefold compared to younger patients. Another reason for the relatively low drug expenditure in the Netherlands is the share of generic drugs (57%).

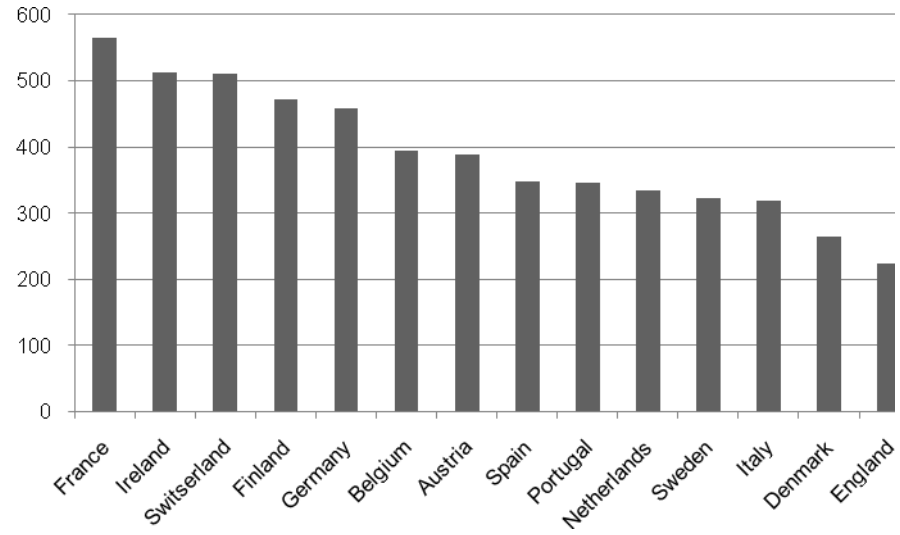


Figure 1. Pharmaceutical costs (euro's) in Europe per person per year

Drug expenditure, covered by healthcare insurance, provided by Dutch pharmacies in 2009 was € 4.789 million. This is € 47 million (1%) higher than in 2008. In 2008, drug expenditure was increased with 1.9% to an amount of € 4.742 million. In the years before 2007 the pharmaceutical expenditure on average increased with 6% each year. Expensive drugs were defined, by the Stichting

Farmaceutische Kentallen (SFK), as drugs for which costs of a prescription exceed €500. The total expenditure on expensive drugs in 2009 rose by €136 million to €988 million, an increase of 16%. The share of expensive drugs in total drug expenditure increased from 6.9% in 2002 to 20.7% in 2009. TNF inhibitors are used for treatment of immune mediated inflammatory disorders (IMID). The expenditure of the TNF inhibitor adalimumab (Humira®) increased by 37% in 2009, reaching € 148 million. The expenditure of the TNF inhibitor etanercept (Enbrel®) increased by 17% in 2009, reaching € 129 million. Data on the recently introduced TNF inhibitor golimumab are not yet available. Adalimumab and etanercept are on top of the list of pharmaceutical expenditures 2009, numbers 1 and 3, respectively (see table below). Due to the increased spending of € 40 and € 19 million of these drugs in 2009, respectively, they are the major contributors to the increased costs of total drug expenditure in 2009. Infliximab is available through the hospital and since June 2007 infliximab is, under restricted conditions, available through " Zelfstandige behandel combinaties (ZBC's). Only in ZBCs infliximab is covered by the GVS, if its provided by the hospital the costs are part of the hospital budget. In 2008 hospital spend € 78,1 million on infliximab, an increase of € 8,7 million, and infliximab is the number one drug in the hospital budgets. The increase in 2006 and 2007 was €15 million each year, due to the coverage of the GVS the increase in 2008 was less than the years before. Sound comparisons of the expenditure of TNF blockers with other European countries are, unfortunately, not possible. .

These numbers represent the overall expenditure of certain drugs, including all indications. No data are available to estimate what part of the total costs per drug is contributed to the treatment of RA. Due to the limited abilities of data registration in hospital and local pharmacies it is difficult to gain information about what amount is contributed to each indication. Therefore, we analysed the data from are own registries, the relative portion of patients treated with TNF blockers is 66, 19 and 15% for RA, SA and PsA, respectively. Data about what specific TNF inhibitor contributes to the cost per indication are not available.The expenditure of TNF blockers in other European countries is not readily available.

Table: Top 10 of pharmaceutical expenditures in the Netherlands 2009

	Generic name (listing 2008)	Brand name	Indication	expenditure in milion € †
1	Adalimumab (5)	Humira	Rheumatic diseases	148 (+37%)
2	Atorvastatine (1)	Lipitor	Lipid lowering	146 (-12%)
3	Etanercept (4)	Enbrel	Rheumatic diseases	129 (+17%)
4	Salmeterol plus fluticason (2)	Seretide	Pulmonary diseases	122 (-1%)
5	Pantoprazol (3)	Pantozol	Gastroprotection	80 (-31%)
6	Tiotropium (6)	Spiriva	Pulmonary diseases	76 (+11%)
7	Esomeprazol (9)	Nexium	Gastroprotection	70 (+11%)
8	Metropolol (8)	Selokeen	Angina pectoris, hypertension, heartfailure	66 (+5%)
9	Formoterol plus budesonide (10)	Symbicort	Pulmonary diseases	64 (+5%)
10	Somatropine (-)	divers	Growth hormone	58 (+7%)

†Between brackets behind the expenditure is the raise in expenditure compared to 2008

7) Generic products

While the patent on Enbrel® expires on October 23, 2012 in the United States (www.uspto.gov/patents/resources/terms/156.html), it is unlikely that a generic will be available at that time. As a biologic, etanercept is subject to different laws than chemical formulations. Currently many countries, including the United States, do not permit the manufacture of generic biologicals. However, the European Union does currently have in place a system to approve generic biologicals (biosimilars) which "requires mandatory clinical testing and periodic review". Biosimilars or follow-on biologics are terms used to describe officially-approved subsequent versions of innovator biopharmaceutical products made by a different sponsor following patent and exclusivity expiry on the innovator product. Unlike the more common small-molecule drugs, biologics generally exhibit high molecular complexity, and may be quite sensitive to manufacturing process changes. The follow-on manufacturer does not have access to the originator's molecular clone and original cell bank, nor to the exact fermentation and purification process, nor to the active drug substance. They do have access to the commercialized innovator product. Differences in impurities and/or breakdown products can have serious health implications. The same concern applies to the reference product when manufacturing changes are made. Small distinctions in the cell line, the manufacturing process or the surrounding environment can make a major difference in side effects observed during treatment, i.e. two similar biologics can trigger very different immunogenic response. Therefore, and unlike chemical pharmaceuticals, substitution between biologics, including biosimilars, can have clinical consequences and does create putative health concerns. Consequently only a few subsequent versions of biologics have been authorized in the US through the simplified procedures allowed for small molecule generics, namely Menotropins (January 1997) and Enoxaparin (July 2010), and a further eight biologics through the so-called 505(b)(2) pathway. The European regulatory authorities led with a specially-adapted approval procedure to authorize subsequent versions of previously approved biologics, termed "similar biological medicinal products" - often called biosimilars for short. This procedure is based on a thorough demonstration of "comparability" of the "similar" product to an existing approved product. Currently (December 2009), ambiguities concerning naming, regional differences in prescribing practices, regional differences in legally defined rules with respect to substitution are important points that still need to be resolved to ensure a safe use of biosimilars. (Source: www.wikipedia.org, verified December 22nd, 2010)

8) Economic evaluations

Methods

A systematic search was performed to retrieve all published systematic reviews of health economic evaluations and cost-effectiveness analyses of treatment of AS in which at least one of the four TNF-alpha blocking agents was investigated. For the search strategy see appendix B. If there was no systematic review or original cost-effectiveness analysis identified, we searched the internet for reports in Dutch or English language published by national governmental organizations. Data that were not presented in Euro's were converted using the exchange rates used by the European central bank of December 21st , 2010.

Outcomes

We retrieved incremental cost effectiveness ratio's (ICER), which reflect the incremental costs per quality adjusted life-year (QALY) or per incremental clinical outcome for each TNF-alpha blocking agent compared with an alternative therapy.

Results

Of the 12 publications that were identified, three were recent systematic reviews. (10;48;49). One of these reviews was excluded because the authors only investigated costs of illness and treatment but did not report data with respect to full economic evaluations. (49) Mcleod et al. presented results of a systematic review of economic evaluations of adalimumab, etanercept and infliximab for patients with AS. (10) In this review all publications on cost-effectiveness of adalimumab, etanercept and infliximab that were published until November 2005 were included. In this review, a total of six economic evaluations were included, of which only two were full papers. (50;51) The other four were abstracts and the information presented was not sufficient to serve as a source for our report. The two full papers presented data on infliximab and etanercept but not on adalimumab. In the second systematic review only one economic evaluation about patients with AS was included. (52) For adalimumab an individual publication of an economic evaluation was used. (53)

Adalimumab

In 2007 a study on the cost-effectiveness of adalimumab was published. (53) Data were based on a phase 3 study of patients with active AS and an inadequate response to NSAIDs. BASDAI and BASFI scores, costs and health related quality of life were modelled. The analysis focused on the cost-effectiveness of adalimumab when used according to the existing guidelines in the United Kingdom. The guidelines recommend that patients who respond well to therapy continue treatment whereas patients who do not respond well to therapy stop. The analysis used time periods of 48 weeks, 5 years

and 30 years. A sensitivity analysis was performed to estimate uncertainty surrounding the estimated ICER that was calculated for the 30 years time period.

Adalimumab (monotherapy) vs. DMARDs

It was estimated that the ICER of adalimumab versus conventional therapy improved with longer time horizons. The 30 year ICER of adalimumab versus conventional therapy was € 27,163 per QALY. The gain in QALYs was 1.03 for every patient started with adalimumab compared to conventional therapy. When indirect costs also were included -which is relevant from a societal perspective – the ICER improved to € 5,990 per QALY. To indicate the importance of the time frame used. The ICER estimated over a 48 weeks period was € 55,274.

Etanercept

Mcleod et al published a review of economic evaluations of etanercept for AS Only one of the included studies reported data on etanercept. Therefore, we used this individual economic evaluation of Boonen et al. as a source of our report. (50) In this publication data from trials performed in the Netherlands and Dutch costs were used as input parameters.

Etanercept vs. DMARDs

Boonen et al. estimated an incremental cost utility ratio (ICUR) of etanercept compared to usual care over a five-year time frame of € 118,022 per QALY gained. (50) Over a five-year period the gain in QALYs of etanercept compared to usual care was 0.27 The sensitivity analyses showed that the ICUR of etanercept compared to usual cary varied from € 42,914 (best case, with probabilities, costs and utilities, but no response in health status with usual care) to € 123,761 (reference case, with two year time horizon).

Infliximab

In the aformentioned study of Boonen et al. also an economic evaluation of infliximab was presented.

Infliximab vs. DMARDs

Boonen et al. estimated an ICUR of infliximab compared to usual care over a five-year time frame of € 189,564 per QALY gained. (50) Over a five-year period the gain in QALYs of infliximab compared to usual care was 0.22. The sensitivity analyses showed that the ICUR of etanercept compared to usual cary varied from € 67,207 (best case, with probabilities, costs and utilities, but no response in health status with usual care) to € 237,010 (reference case, with two year time horizon). Kobelt et al. estimated over a two year time period an ICER of infliximab compared to placebo of € 41,632,- per QALY gained (51) Over a two-year period the gain in QALYs of infliximab compared to placebo was 0.18. For the a longer time period the ICER was € 11,290 per QALY gained.

Overall conclusion

The cost-effectiveness reported in the studies of Boonen et al. and Kobelt et al. varied from an ICER of € 189,564 per QALY to € 41,632,- per QALY, respectively. This difference might be due to the way in which the costs of the control arm were calculated. Kobelt et al. estimated the total costs for placebo therapy four times higher than Boonen et al. did for costs of usual care. However, Boonen et al. used Dutch costs data while Kobelt et al. used Canadian data. The higher ICERs that are shown in the publication of Boonen et al. might be the result of the relatively small improvement in QALYs when therapy with infliximab compared to control between the two studies is compared. This can be caused by the difference in disease activity of the hypothetical cohort of patients used in the model. In the model of Kobelt et al the disease activity was significantly higher compared to the model of Boonen et al. (BASDAI 5.5 versus 4.0). Therapy with anti-TNF-alpha leads to a higher absolute reduction in patients with higher disease activity in comparison to patients with a lower disease activity. Moreover,the time-frame of the two models differed. Kobelt et al. model a time period of 30 years, whereas the time period that was model by Boonen et al. was only 5 years. Different assumptions regarding the effectiveness of therapy in this period might result in differences in ICER when the two models are compared. In a sensitivity analyses of Kobelt et al. it was shown that the ICER increases by 60 – 100% if the timeframe that was modelled was doubled. Finally,differences in how the two healthcare-systems are financed can partly explain the differences in the reported ICERs. The study by Boonen et al. appears more relevant for the Dutch health care system.

Golimumab

To our knowledge, no adequate economic evaluation on golimumab for therapy of AS has been published, thus far. However, globally the efficacy of golimumab in the treatment of AS is comparable to that of infliximab and etanercept. The costs of therapy with golimumab do not remarkably differ from the costs of etanercept. Combining these two observations might suggest that the cost-effectiveness of golimumab in relation to etanercept for therapy of AS might be comparable to the cost-effectiveness of golimumab in RA in relation to etanercept and adalimumab. Obviously, a methodologically sound cost-effectiveness analysis of golimumab should be performed before firm conclusions regarding the cost-effectivieness of golimumab can be reached

Overall conclusion

The validity of economic evaluations of therapy with TNF-alpha inhibitors is limited by insufficient insight in the natural course of the disease and long term effectiveness and safety of the therapy. The ICER estimated in the economic evaluation of adalimumab appeared to be lower those of etanercept and infliximab. These differences might be the result of some important methodological differences between the economic evaluations. For example, the different time frames that were used. As more

non-responders stop using medication when a longer time horizon is used, the proportion of patients for whom therapy is effective increases, resulting in an increase in cost-effectiveness. Therefore, the time frame of 30 years used in the economic evaluation of adalimumab might explain the favourable ICER for adalimumab. It was also reported that the ICER of adalimumab versus conventional therapy improves with longer time horizons. This is not only important from a methodological point of view but is also important taking the age of onset of AS into account. Since in general the onset of AS is at a much younger age than for example in RA, this has consequences for the outcomes of cost-effectiveness analyses. In addition, it is expected that due to introduction of additional agents in combination with the impact of market forces the costs of TNF-alpha blockings agents will go down. (50;54;54)

9) Ongoing studies

Presently there are several, small scaled, registries in e.g. Spain (ESPIDEP), South Sweden and Czech (ATTRA). However, due to the limited number of patients studied, the results were not incorporated in our present report.

10) Unexplored areas

There are several options for a future research agenda:

1. Considering the variable response to TNF-blocking therapy and the high cost of treatment, it is necessary to predict the response of patients to treatment using novel biomarkers, such as genetic markers or gene expression patterns. At present, however, there are no biomarkers with reproducible predictive ability for response. Even when these are found, it is uncertain whether a prediction at an individual level will be possible, which is a prerequisite for true personalized medicine.
2. Direct comparison of TNF blockers with each other or with other biologicals as first or second biological. Until now, such trials have not been published.
3. The response to other biologicals, preferably relative to the response to TNF blockade.
4. Effect of stopping or dose decrease of TNF blockers in case of sustained remission. This could be performed within rheumatology networks.
5. Reducing the effect of immunogenicity of these TNF-alpha inhibitors by concomitantly prescribing immunomodulators thereby increasing the treatment effect.

11) Research into unexplored areas

Immunogenicity of TNF inhibitors

Biologicals that block TNF are powerful modalities in the treatment of various inflammatory diseases, however, both chimeric and human biologicals can induce anti-drug antibodies.

Immunogenicity can change the pharmacokinetics of biological therapeutics resulting in suboptimal therapeutic levels of the drug in patient's serum. The problem of immunogenicity against TNF inhibitors has been described since these biologicals are on the market for the treatment of various inflammatory diseases, and the knowledge regarding these anti-drug antibodies is increasing. Nevertheless, technical factors, standardisation of the assays used to measure anti-drug antibodies and the timing of the measurements make immunogenicity a complex subject to investigate and hampers the translation into clinical practice. (55)

Relevance of anti-drug antibodies

In studies where trough serum adalimumab or infliximab concentrations were measured, the presence of anti-drug antibodies was associated with decreased serum drug levels and a diminished response.(56-63)

Furthermore, anti-drug antibodies in the presence of TNF inhibitor levels lead to the formation of immune complexes. (64) The continuous presence of immune complexes in the serum could lead to adverse events. Little is known about the safety of drug-anti-drug antibody immune complexes. The presence of antibodies to infliximab and of immune complexes of various sizes might be associated with infusion-related hypersensitivity reactions.

Prevalence of anti-drug antibodies

In AS, studies on the effect of immunogenicity on treatment response to anti-TNF therapy are limited and those studies comprise a small number of patients. In three studies by the same group, anti-drug antibodies to adalimumab, infliximab and etanercept were detected in 31%, 29% and 0%, respectively.(65-67) Antibody formation was associated with ASAS20 non-response and/or diminishing drug levels in patient's blood. In another study, anti-drug antibodies were detected in 30%, 20% and 0% of adalimumab, infliximab and etanercept treated AS patients, respectively. (68) In this study also, the presence of antibodies against infliximab and adalimumab was associated with decreased efficacy of the drug and with early treatment discontinuation. Although MTX itself appeared not to be effective in AS patients, it might be an important concomitant immunosuppressant helping to counteract immunogenicity of TNF inhibitors, because in larger studies in RA, Crohn's disease and juvenile idiopathic arthritis, co-treatment with immunomodulators like methotrexate and azathioprine lowered the anti-drug antibody formation and the efficacy of adalimumab and infliximab was increased. (55)

Cardiovascular disease

The excess mortality in AS is largely due to cardiovascular disease, particularly of atherosclerotic origin such as ischemic heart disease. (69) Cardiovascular morbidity in AS patients is also elevated by at least twofold in comparison to the general population and appears to be comparable to RA (70;71) The last decade it has become widely acknowledged that inflammation plays a pivotal role throughout all stages of atherogenesis and hence the chronic inflammatory process in AS renders these patients more susceptible to atherosclerotic disease. Vice versa one would expect that suppression of the inflammatory process by TNF-blockers will lead to a lower cardiovascular risk. In RA a systematic review and meta-analysis, encompassing 16 observational and RCTs, indicated that TNF-blocking therapy was associated with a reduced risk for (all) cardiovascular events (RR: 0.46; [95%CI: 0.28-077]). (72) Thus far similar data for AS are not available. However, in view of the similar etiology of accelerated atherosclerosis in both RA and AS, similar beneficial effects of TNF-blockers on the cardiovascular risk in AS might be anticipated. Obviously, confirmatory studies are needed before this aspect can be taken into account in clinical decision making regarding the necessity of TNF-blockers.

12) Input of patients

Patient organisations such as the *Reumapatiëntenbond* have not voiced opinions on the treatment with biologicals, other than a letter to the Minister of Health in August, 2010, together with the *Reumafonds* and the *Nederlandse Vereniging voor Reumatologie* (NVR), in which they expressed concerns about the ongoing availability of TNF blockers for patients with rheumatic diseases, should the planned budget cuts in 2011 become reality. Data on the patient perspective are not abundant for treatment with TNF blockers in AS and are provided in the quality of life chapter.

13) Input of pharmacists

The distribution of TNF blockers is presently performed by hospital pharmacies for the intravenously administered infliximab, and by nationally operating specialized pharmacies, with separate companies for each of the four subcutaneously administered, TNF blockers. There are a few exceptions such as *Reade* and the *Maartenskliniek,* both specialized hospitals for musculoskeletal diseases, that distribute subcutaneous drugs themselves, and some local pharmacies that provide for individual patients. If these drugs are to be financed through the hospital budget, as is foreseen for mid-2011, the hospitals will become responsible for the distribution, which may lead to new ways of distribution by pharmacies.

In a letter to the minister of Health dated July 20, 2010, the *Nederlandse Vereniging van Ziekenhuisapothekers* (NVZA) and the *Nederlandse Vereniging voor Poliklinische Farmacie* (NVPF)

stated that they are willing to contribute to the efficient use of TNF blockers provided that this has no relevant consequences for the availability of these drugs. In addition, they support the plan that control and accountability for the costs will become the responsibility of the hospitals. Furthermore, these pharmacist societies as well as the Nederlandse Vereniging van Reumatologie (NVR) have voiced concerns about the potential jeopardizing of the availability of TNF blockers for rheumatology patients in case the costs of these drugs become part of the hospital budget in combination with a reduced financial compensation, as is presently planned by the Ministry of Health. In December 2010 in a letter of the *Nederlandse Vereniging van Ziekenhuizen* (NVZ), supported by the NVZA, these concerns were expressed again. To ensure optimal health care for patients using TNF blockers, a sound financial and practical plan from the Ministry of Health is mandatory. The Ministry of Health has stated that current patient care and distribution of these drugs needs to be organized by the hospitals. In addition to the planned savings extra services are expected from the hospitals without additional financial support. All involved branch organizations feel that these goals of the Ministry of Health are not realistic and need to be reconsidered.

Reference List

(1) *Khan MA. Clinical features of ankylosing spondylitis. Rheumatology, third edition, Hochberg et al. eds. Mosby 2003; 1161-1181. 2003.*

(2) *Zochling J, van der HD, Burgos-Vargas R, Collantes E, Davis JC, Jr., Dijkmans B et al. ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2006;65:442-52.*

(3) *Maini RN, Elliott M, Brennan FM, Williams RO, Feldmann M. Targeting TNF alpha for the therapy of rheumatoid arthritis. Clin Exp Rheumatol. 1994;12 Suppl 11:S63-S66.*

(4) *Saad AA, Ashcroft DM, Watson KD, Symmons DPM, Noyce PR, Hyrich KL. Improvements in quality of life and functional status in patients with psoriatic arthritis receiving anti-tumor necrosis factor therapies. Arthritis Care Res (Hoboken). 2010;62:345-53.*

(5) *Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009;68 Suppl 2:ii1-44.*

(6) *van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361-68.*

(7) *Anderson JJ, Baron G, van der HD, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum. 2001;44:1876-86.*

(8) *Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994;21:2281-85.*

(9) *van der LS, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361-68.*

(10) *McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. Health Technol Assess. 2007;11:1-iv.*

(11) *Kay J, Rahman MU. Golimumab: A novel human anti-TNF-alpha monoclonal antibody for the treatment of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. Core Evid. 2010;4:159-70.*

(12) *Fouque-Aubert A, Jette-Paulin L, Combescure C, Basch A, Tebib J, Gossec L. Serious infections in patients with ankylosing spondylitis with and without TNF blockers: a systematic review and meta-analysis of randomised placebo-controlled trials. Ann Rheum Dis. 2010;69:1756-61.*

(13) *Maksymowych WP, Rahman P Keystone E Wong R Inman R. Efficacy of adalimumab in active ankylosing spondylitis (AS) - results ot the Canadian AS study. Arthritis Rheum 2005 52(505). 2005.*

(14) *van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BAC, Braun J et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2006;54:2136-46.*

(15) *van der Heijde, D., Luo, M. P., Matsumoto A, Mease, P. J., Torre-Alonso j, Wordsworth, P., and et al. Adalimumab improves health-related quality of life in patients with active ankylosing spondylitis - the ATLAS trial. Arthritis Rheum 2005 52(S211). 2005.*

(16) *Brandt J, Khariouzov A, Listing J, Haibel H, Sorensen H, Grassnickel L et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum. 2003;48:1667-75.*

(17) *Calin A, Dijkmans BAC, Emery P, Hakala M, Kalden J, Leirisalo-Repo M et al. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis. 2004;63:1594-600.*

(18) *Davis JC, Jr., van der HD, Braun J, Dougados M, Cush J, Clegg DO et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum. 2003;48:3230-3236.*

(19) *Gorman JD, Sack KE, Davis JC, Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med. 2002;346:1349-56.*

(20) *Wyeth Pharmaceuticals. Manufacturer submission to the National Institute for Health and Clinical Excellence. National Institute for Health and Clinical Excellence . 2006.*

(21) *van der Heijde D, Da Silva JC, Dougados M, Geher P, van der Horst-Bruinsma I, Juanola X et al. Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis. Ann Rheum Dis. 2006;65:1572-77.*

(22) *Braun J, Brandt J, Listing J, Zink A, Alten R, Golder W et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet. 2002;359:1187-93.*

(23) *van der Heijde DM, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum. 2005;52:582-91.*

(24) *Inman RD, Davis JC, Jr., Heijde D, Diekman L, Sieper J, Kim SI et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum. 2008;58:3402-12.*

(25) *Inman RD, Davis JCJ, Heijde Dvd, Diekman L, Sieper J, Kim SI et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum. 2008;58:3402-12.*

(26) *Nederlandse Vereniging van Reumatologie. Richtlijn voor de diagnostiek en behandeling van Ankyloserende Spondylitis. Nederlandse Vereniging van Reumatologie. 2009.*

(27) *Nederlandse Vereniging van Reumatologie. Standpunt cq behandeladvies voor het toepassen van TNFblokkade in de behandeling sponylitis ankylopetica (ziekte van Bechterew). herziening 2005.*

(28) *Werkgroep Richtlijn Spondylitis Ankylopoetica, Nederlandse Vereniging Reumatologie. Richtlijn voor de diagnostiek en behandeling van Ankyloserende Spondylitis. 2010.*

(29) *Nederlandse Vereniging voor Reumatologie. Concept Guideline NVR; Goed en verantwoord gebruik van biologicals. 2010.*

(30) *Heiberg MS, Kaufmann C, Rodevand E, Mikkelsen K, Koldingsnes W, Mowinckel P et al. The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6 month results from a longitudinal, observational, multicentre study. Ann Rheum Dis. 2007;66:1038-42.*

(31) *Konttinen L, Tuompo R, Uusitalo T, Luosujarvi R, Laiho K, Lahteenmaki J et al. Anti-TNF therapy in the treatment of ankylosing spondylitis: the Finnish experience. Clin Rheumatol. 2007;26:1693-700.*

(32) *Kristensen LE, Gulfe A, Saxne T, Geborek P. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. Ann Rheum Dis. 2008;67:364-69.*

(33) *Saad AA, Ashcroft DM, Watson KD, Symmons DP, Noyce PR, Hyrich KL. Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford). 2010;49:697-705.*

(34) *Setoguchi S, Solomon DH, Weinblatt ME, Katz JN, Avorn J, Glynn RJ et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum. 2006;54:2757-64.*

(35) *Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheum. 2007;56:2886-95.*

(36) *Askling J, et al. No increase in overall risk for cancer in RA treated with TNFantagonists, but risks for certain cancer types may be elevated. Rheum Dis 66, 54. 2007.*

(37) *Verstappen SM, Boonen A, Bijlsma JW, Buskens E, Verkleij H, Schenk Y et al. Working status among Dutch patients with rheumatoid arthritis: work disability and working conditions. Rheumatology (Oxford). 2005;44:202-6.*

(38) *Keat AC, Gaffney K, Gilbert AK, Harris C, Leeder J. Influence of biologic therapy on return to work in people with work disability due to ankylosing spondylitis. Rheumatology (Oxford). 2008;47:481-83.*

(39) *Barkham N, Coates LC, Keen H, Hensor E, Fraser A, Redmond A et al. Double-blind placebo-controlled trial of etanercept in the prevention of work disability in ankylosing spondylitis. Ann Rheum Dis. 2010;69:1926-28.*

(40) *Maksymowych WP, Gooch KL, Wong RL, Kupper H, van der HD. Impact of age, sex, physical function, health-related quality of life, and treatment with adalimumab on work status and work productivity of patients with ankylosing spondylitis. J Rheumatol. 2010;37:385-92.*

(41) *van der HD, Han C, DeVlam K, Burmester G, van den BF, Williamson P et al. Infliximab improves productivity and reduces workday loss in patients with ankylosing spondylitis: results from a randomized, placebo-controlled trial. Arthritis Rheum. 2006;55:569-74.*

(42) *Davis JC, van der Heijde D, Dougados M, Woolley JM. Reductions in health-related quality of life in patients with ankylosing spondylitis and improvements with etanercept therapy. Arthritis Rheum. 2005;53:494-501.*

(43) *Braun J, McHugh N, Singh A, Wajdula JS, Sato R. Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. Rheumatology (Oxford). 2007;46:999-1004.*

(44) *Boonen A, Patel V, Traina S, Chiou CF, Maetzel A, Tsuji W. Rapid and sustained improvement in health-related quality of life and utility for 72 weeks in patients with ankylosing spondylitis receiving etanercept. J Rheumatol. 2008;35:662-67.*

(45) *Ertenli I, Ozer S, Kiraz S, Apras SB, Akdogan A, Karadag O et al. Infliximab, a TNF-alpha antagonist treatment in patients with ankylosing spondylitis: the impact on depression, anxiety and quality of life level. Rheumatol Int. 2010.*

(46) *Deodhar A, Braun J, Inman RD, Mack M, Parasuraman S, Buchanan J et al. Golimumab reduces sleep disturbance in patients with active ankylosing spondylitis: results from a randomized, placebo-controlled trial. Arthritis Care Res (Hoboken). 2010;62:1266-71.*

(47) *Rudwaleit M, Gooch K, Michel B, Herold M, Thorner A, Wong R et al. Adalimumab Improves Sleep and Sleep Quality in Patients with Active Ankylosing Spondylitis. J Rheumatol. 2010.*

(48) *Fleurence R, Spackman E. Cost-effectiveness of biologic agents for treatment of autoimmune disorders: structured review of the literature. J Rheumatol. 2006;33:2124-31.*

(49) *Franke LC, Ament AJHA, Van De Laar MAFJ, Boonen A, Severens JL. Cost-of-illness of rheumatoid arthritis and ankylosing spondylitis. Clin Exp Rheumatol. 2009;27:S118-S123.*

(50) *Boonen A, van der HD, Severens JL, Boendermaker A, Landewe R, Braun J et al. Markov model into the cost-utility over five years of etanercept and infliximab compared with usual care in patients with active ankylosing spondylitis. Ann Rheum Dis. 2006;65:201-8.*

(51) *Kobelt G, ndlin-Sobocki P, Maksymowych WP. The cost-effectiveness of infliximab (Remicade) in the treatment of ankylosing spondylitis in Canada. J Rheumatol. 2006;33:732-40.*

(52) *Kobelt G, ndlin-Sobocki P, Brophy S, Jonsson L, Calin A, Braun J. The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade). Rheumatology (Oxford). 2004;43:1158-66.*

(53) *Botteman MF, Hay JW, Luo MP, Curry AS, Wong RL, van Hout BA. Cost effectiveness of adalimumab for the treatment of ankylosing spondylitis in the United Kingdom. Rheumatology (Oxford). 2007;46:1320-1328.*

(54) *Kavanaugh A. The pharmacoeconomics of newer therapeutics for rheumatic diseases. Rheum Dis Clin North Am. 2006;32:45-56, viii.*

(55) *Krieckaert CL, Bartelds GM, Lems WF, Wolbink GJ. The effect of immunomodulators on the immunogenicity of TNF-blocking therapeutic monoclonal antibodies: a review. Arthritis Res Ther. 2010;12:217.*

(56) *Baert, F. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. Noman, M., Vermeire, S., Van Assche, G., D'Haens, G., Carbonez, A, and Rutgeerts, P. N Engl J Med 348, 601-608.*

(57) *Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. Ann Rheum Dis. 2007;66:921-26.*

(58) *Bendtzen K, Geborek P, Svenson M, Larsson L, Kapetanovic MC, Saxne T. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab. Arthritis Rheum. 2006;54:3782-89.*

(59) *Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359:1541-49.*

(60) *Karmiris K, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. Gastroenterology. 2009;137:1628-40.*

(61) *Radstake TRDJ, Svenson M, Eijsbouts AM, van den Hoogen FHJ, Enevold C, van Riel PLCM et al. Formation of antibodies against infliximab and adalimumab strongly*

correlates with functional drug levels and clinical responses in rheumatoid arthritis. Ann Rheum Dis. 2009;68:1739-45.

(62) Vermeire S, Noman M, Van Assche G, Baert F, D'Haens G, Rutgeerts P. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. Gut. 2007;56:1226-31.

(63) Wolbink GJ, Vis M, Lems W, Voskuyl AE, de Groot E, Nurmohamed MT et al. Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis Rheum. 2006;54:711-15.

(64) van der Laken CJ, Voskuyl AE, Roos JC, Stigter vW, de Groot ER, Wolbink G et al. Imaging and serum analysis of immune complex formation of radiolabelled infliximab and anti-infliximab in responders and non-responders to therapy for rheumatoid arthritis. Ann Rheum Dis. 2007;66:253-56.

(65) de Vries MK, Wolbink GJ, Stapel SO, de Vrieze H, van Denderen JC, Dijkmans BA et al. Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation. Ann Rheum Dis. 2007;66:1252-54.

(66) de Vries MK, Brouwer E, van der Horst-Bruinsma IE, Spoorenberg A, van Denderen JC, Jamnitski A et al. Decreased clinical response to adalimumab in ankylosing spondylitis is associated with antibody formation. Ann Rheum Dis. 2009;68:1787-88.

(67) de Vries MK, van der Horst-Bruinsma IE, Nurmohamed MT, Aarden LA, Stapel SO, Peters MJ et al. Immunogenicity does not influence treatment with etanercept in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68:531-35.

(68) Arends S, Lebbink HR, Spoorenberg A, Bungener LB, Roozendaal C, van d, V et al. The formation of autoantibodies and antibodies to TNF-alpha blocking agents in relation to clinical response in patients with ankylosing spondylitis. Clin Exp Rheumatol. 2010;28:661-68.

(69) Peters MJ, van der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT. Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. Semin Arthritis Rheum. 2004;34:585-92.

(70) Peters MJ, van Eijk IC, Smulders YM, Serne E, Dijkmans BA, van der Horst-Bruinsma IE et al. Signs of accelerated preclinical atherosclerosis in patients with ankylosing spondylitis. J Rheumatol. 2010;37:161-66.

(71) Peters MJ, Visman I, Nielen MM, Van Dillen N, Verheij RA, van der Horst-Bruinsma IE et al. Ankylosing spondylitis: a risk factor for myocardial infarction? Ann Rheum Dis. 2010;69:579-81.

(72) Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: Anti-tumor necrosis factor alpha therapy and cardiovascular events in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2010.

Appendix A: author biographies

Daan Jansen (1979) received his degree in pharmacy at Utrecht University and has worked as a pharmacist since 2008. At Reade he is head of the specialized rheumatology pharmacy since 2009, which serves 10.000 outpatients per year as well as the large day clinic for intravenous biologics treatment. (no conflict of interest)

Carlo van Dongen (1971) received his degree in Medicine and in Human Movement Science. His thesis was entitled "an evidence based approach to optimizing anticoagulant therapy" . Since 2009 he is head of the department of Research of Reade (formerly the Jan van Breemeninstituut). His current research interest is the epidemiology of rheumatic diseases. (no conflict of interest)

Sidney Rubinstein performs systematic reviews of medical and non-medical treatment of chronic low back pain. Currently he supervises a PhD student who investigates neck and low back pain in patients during treatment by a chiropractor. (no conflict of interest)

Charlotte Krieckaert gained her medical degree in 2009 from the VU University Medical Center in Amsterdam, the Netherlands. Currently she is working on a PhD in rheumatology on immunogenicity to biologicals at Reade/ Jan van Breemen Research Institute, Amsterdam. (no conflict of interest)

Gertjan Wolbink is rheumatologist and researcher at Reade and Sanquin Immunopathology. His fields of research include the pathogenesis of RA, immunogenicity, the mechanism of action of biologicals and genetics. He is member of the Amsterdam genetics in RA platform (GENRA) and member of the European Immunogenicity Platform. His H-index is 21. Disclosure: he leads a project to investigate the role of immunogenicity in the treatment of RA with TNF blocking agents (Funding €1.7 million by Pfizer).

Maurits van Tulder is professor of Health Technology Assessment at the Department of Health Sciences of the VU University Amsterdam, the Netherlands. He is co-editor of the Cochrane Collaboration Back Review Group (www.cochrane.iwh.on.ca). He is author of more than 200 scientific papers in peer reviewed international journals, of which many report systematic reviews and economic evaluations of diagnostic and therapeutic interventions. His H-index is 36. He is also involved in courses on systematic reviews in Master programs of Health Sciences and Epidemiology at the VU University and at the University of Toronto, Canada. (no conflict of interest)

Dirkjan van Schaardenburg (1956) specialized in internal medicine and rheumatology at Leiden University Hospital. He became Head of the Department of Rheumatology at the Jan van Breemen Institute in Amsterdam in 1994 and Head of the Division of Rheumatology of Reade in 2009. He is also affiliated with the Department of Rheumatology of the VU University Medical Center. His research interests are early and preclinical rheumatoid arthritis. Disclosure: project leader of an investigator driven study of aggressive therapy including adalimumab for oligoarthritis funded by Abbott, the 'STREAM' study (€160.000).

Michael Nurmohamed (1958) qualified as an epidemiologist in 1995 and as rheumatologist in 2000. From 2000 onwards he worked as a rheumatologist and researcher at the department of Rheumatology, Jan van Breemen Institute (JBI) and the departments of Rheumatology and Internal Medicine of the VU University Medical Center, Amsterdam. From 2009 onwards he is also the Director of the Division Research and Education at the JBI. His main scientific interest includes cardiovascular co-morbidity in rheumatic diseases. He has authored or co-authored about 160 publications in, primarily peer-reviewed, journals and several book chapters, had around 150 presentations at (international) scientific meetings and is regular reviewer of several international journals and an editorial board member of the Annals of Rheumatic Diseases. Disclosure: The Jan van Breemen Research Institute has received research grants from: BMS, MSD-Scheringh Plough, Abbott, Pfizer, UCB, Roche. Dr Nurmohamed has received speaker's fees and has served, on an ad hoc basis, in several advisory boards.

Appendix B: Search strategy

PubMed

#1 Ziekte van Bechterew
"Spondylitis, Ankylosing"[Mesh] OR Bechterew*[tiab] OR "Ankylosing Spondyloarthritis"[tiab] OR "Ankylosing Spondylarthritis"[tiab] OR "Ankylosing Spondylitis"[tiab] OR "Rheumatoid Spondylitis"[tiab] OR "Spondylarthritis Ankylopoietica"[tiab] OR "Marie-Struempell Disease"[tiab]

#2 Geneesmiddelen
"TNF {alpha}"[tiab] OR "anti TNF"[tiab] OR TNFalpha[tiab] OR "infliximab "[Substance Name] OR infliximab[tiab] OR Remicade[tiab] OR "adalimumab"[Substance Name] OR "adalimumab"[tiab] OR Humira[tiab] OR "TNFR-Fc fusion protein"[Substance Name] OR etanercept[tiab] OR Enbrel[tiab] OR "golimumab"[Substance Name] OR golimumab[tiab] OR Simponi[tiab] OR "CDP870"[Substance Name] OR certolizumab[tiab] OR cimzia[tiab]

#3 Cost effectivity, efficacy, QOL
Efficacy[tiab] OR "Treatment Outcome"[Mesh] OR "Drug Toxicity"[Mesh] OR safety[tiab] OR "Costs and Cost Analysis"[Mesh] OR cost[tiab] OR economic*[tiab] OR "Quality of Life"[Mesh] OR "Quality of Life"[tiab] OR QOL[tiab] OR "Quality adjusted"[tiab]

#3 (R)CT en Review filter
(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR "clinical trial" [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR "latin square" [tw] OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [pt] OR evaluation studies [pt] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control[tw] OR controll*[tw] OR prospectiv* [tw] OR volunteer* [tw]) OR ((review[tiab] OR "Review"[Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR meta-analysis[tiab] OR "Meta-Analysis "[Publication Type]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh]))

 # Publication type
NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "case reports"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type])

#10 Search #9 NOT ("addresses"[Publication Type] OR "biography"[Publication Type] OR "case reports"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type]) 330

#9 Search #7 AND #8 362

#8 Search (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR "clinical trial" [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR "latin square" [tw] OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [pt] OR evaluation studies [pt] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control[tw] OR controll*[tw] OR prospectiv* [tw] OR

volunteer* [tw]) OR ((review[tiab] OR "Review"[Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR meta-analysis[tiab] OR "Meta-Analysis "[Publication Type]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])) 6213896

#7 Search #4 AND #5 AND #6 456

#6 Search Efficacy[tiab] OR "Treatment Outcome"[Mesh] OR "Drug Toxicity"[Mesh] OR safety[tiab] OR "Costs and Cost Analysis"[Mesh] OR cost[tiab] OR economic*[tiab] OR "Quality of Life"[Mesh] OR "Quality of Life"[tiab] OR QOL[tiab] OR "Quality adjusted"[tiab] 1312216

#5 Search "TNF {alpha}"[tiab] OR "anti TNF"[tiab] OR TNFalpha[tiab] OR "infliximab "[Substance Name] OR infliximab[tiab] OR Remicade[tiab] OR "adalimumab"[Substance Name] OR "adalimumab"[tiab] OR Humira[tiab] OR "TNFR-Fc fusion protein"[Substance Name] OR etanercept[tiab] OR Enbrel[tiab] OR "golimumab"[Substance Name] OR golimumab[tiab] OR Simponi[tiab] OR "CDP870"[Substance Name] OR certolizumab[tiab] OR cimzia[tiab] 78192

#4 Search "Spondylitis, Ankylosing"[Mesh] OR Bechterew*[tiab] OR "Ankylosing Spondyloarthritis"[tiab] OR "Ankylosing Spondylarthritis"[tiab] OR "Ankylosing Spondylitis"[tiab] OR "Rheumatoid Spondylitis"[tiab] OR "Spondylarthritis Ankylopoietica"[tiab] OR "Marie-Struempell Disease"[tiab] 12275

EMBASE.com

#1 Ziekte van Bechterew
'ankylosing spondylitis'/exp OR Bechterew*:ti,ab OR 'Ankylosing Spondyloarthritis':ti,ab OR 'ankylosing spondylarthritis':ti,ab OR 'Ankylosing Spondylitis':ti,ab OR 'rheumatoid spondylitis':ti,ab OR 'spondylarthritis ankylopoietica':ti,ab OR 'Marie-Struempell Disease':ti,ab

#2 Geneesmiddelen
'tumor necrosis factor inhibitor'/exp OR 'infliximab'/exp OR 'adalimumab'/exp OR 'etanercept'/exp OR 'golimumab'/exp OR 'certolizumab pegol'/exp

#3 Cost effectivity, efficacy, QOL
efficacy:ti,ab OR 'drug efficacy'/exp OR 'cost effectiveness analysis'/exp OR cost:ti,ab OR economic*:ti,ab OR 'quality of life'/exp OR 'quality of life':ti,ab OR QOL:ti,ab OR 'Quality adjusted':ti,ab

#3 (R)CT en Review filter
'clinical trial'/exp OR 'randomization'/exp OR 'double blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'placebo'/exp OR 'placebo effect'/exp OR placebo* OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR 'Latin square design'/exp OR 'comparative study'/exp OR 'evaluation research'/exp OR 'evaluation and follow up'/exp OR 'prospective study'/exp OR control* OR controll* OR assign* OR allocat* OR volunteer* OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'review'/exp OR 'systematic review'/exp OR 'meta analysis'/exp

Limits: -

Search:
#5 #1 AND #2 AND #3 AND #4 773

#4 'clinical trial'/exp OR 'randomization'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'placebo'/exp OR 'placebo effect'/exp OR placebo* OR (singl* OR doubl* OR trebl* OR tripl* AND (mask* OR blind*)) OR 'latin square design'/exp OR 'comparative study'/exp OR 'evaluation research'/exp OR 'evaluation and follow up'/exp OR 'prospective study'/exp OR control* OR controll* OR assign* OR allocat* OR volunteer* OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'review'/exp OR 'systematic review'/exp OR 'meta analysis'/exp 8,953,101

#3 efficacy:ab,ti OR 'drug efficacy'/exp OR 'cost effectiveness analysis'/exp OR cost:ab,ti OR economic*:ab,ti OR 'quality of life'/exp OR 'quality of life':ab,ti OR qol:ab,ti OR 'quality adjusted':ab,ti 1,294,530

#2 'tumor necrosis factor inhibitor'/exp OR 'infliximab'/exp OR 'adalimumab'/exp OR 'etanercept'/exp OR 'golimumab'/exp OR 'certolizumab pegol'/exp 22,607

#1 'ankylosing spondylitis'/exp OR bechterew*:ab,ti OR 'ankylosing spondyloarthritis':ab,ti OR 'ankylosing spondylarthritis':ab,ti OR 'ankylosing spondylitis':ab,ti OR 'rheumatoid spondylitis':ab,ti OR 'spondylarthritis ankylopoietica':ab,ti OR 'marie-struempell disease':ab,ti 16,215

Cinahl

#1 Ziekte van Bechterew
(MH "Spondylitis, Ankylosing") OR Bechterew* OR "Ankylosing Spondyloarthritis" OR "Ankylosing Spondylarthritis" OR "Ankylosing Spondylitis" OR "Rheumatoid Spondylitis" OR "Spondylarthritis Ankylopoietica" OR "Marie-Struempell Disease"

#2 Geneesmiddelen
(MH "Infliximab") OR (MH "Antibodies, Monoclonal") OR adalimumab OR (MH "Etanercept") OR golimumab OR certolizumab OR remicade OR humira OR simponi

#3 Cost effectivity, efficacy, QOL
(MH "Costs and Cost Analysis") OR (MH "Cost Benefit Analysis") OR (MH "Cost Control") OR efficacy OR cost efficiency OR economic* OR (MH "Safety") OR (MH "Quality of Life") OR "Quality adjusted"

#3 (R)CT en Review filter
Via Limiters => niet nodig gezien geringe aantal

Search:
S4 ((MH "Costs and Cost Analysis") OR (MH "Cost Benefit Analysis") OR (MH "Cost Control") OR efficacy OR cost efficiency OR economic* OR (MH "Safety") OR (MH "Quality of Life") OR "Quality adjusted") and (S1 and S2 and S3) - Search modes - Boolean/Phrase View Results (50)

S3 (MH "Costs and Cost Analysis") OR (MH "Cost Benefit Analysis") OR (MH "Cost Control") OR efficacy OR cost efficiency OR economic* OR (MH "Safety") OR (MH "Quality of Life") OR "Quality adjusted" - Search modes - Boolean/Phrase View Results (175126)

S2 (MH "Infliximab") OR (MH "Antibodies, Monoclonal") OR adalimumab OR (MH "Etanercept") OR golimumab OR certolizumab OR remicade OR humira OR simponi Search modes - Boolean/Phrase - View Results (5981)

S1 (MH "Spondylitis, Ankylosing") OR Bechterew* OR "Ankylosing Spondyloarthritis" OR "Ankylosing Spondylarthritis" OR "Ankylosing Spondylitis" OR "Rheumatoid Spondylitis" OR "Spondylarthritis Ankylopoietica" OR "Marie-Struempell Disease" - Search modes - Boolean/Phrase View Results (882)

Cochrane

#1 Ziekte van Bechterew
"Spondylitis, Ankylosing" OR Bechterew* OR "Ankylosing Spondyloarthritis" OR "Ankylosing Spondylarthritis" OR "Ankylosing Spondylitis" OR "Rheumatoid Spondylitis" OR "Spondylarthritis Ankylopoietica" OR "Marie-Struempell Disease"

#2 Geneesmiddelen
"TNF {alpha}" OR "anti TNF" OR TNFalpha OR "infliximab " OR infliximab OR Remicade OR "adalimumab" OR "adalimumab" OR Humira OR "TNFR-Fc fusion protein" OR etanercept OR Enbrel OR "golimumab" OR golimumab OR Simponi OR "CDP870" OR certolizumab OR cimzia

#3 Cost effectivity, efficacy, QOL
Efficacy OR "Treatment Outcome" OR "Drug Toxicity" OR safety OR cost OR economic* OR "Quality of Life" OR QOL OR "quality adjusted" OR "drug efficacy"

Search:

#1 "Spondylitis, Ankylosing" OR Bechterew* OR "Ankylosing Spondyloarthritis" OR "Ankylosing Spondylarthritis" OR "Ankylosing Spondylitis" OR "Rheumatoid Spondylitis" OR "Spondylarthritis Ankylopoietica" OR "Marie-Struempell Disease" 571

#2 "TNF {alpha}" OR "anti TNF" OR TNFalpha OR "infliximab " OR infliximab OR Remicade OR "adalimumab" OR "adalimumab" OR Humira OR "TNFR-Fc fusion protein" OR etanercept OR Enbrel OR "golimumab" OR golimumab OR Simponi OR "CDP870" OR certolizumab OR cimzia 2777

#3 Efficacy OR "Treatment Outcome" OR "Drug Toxicity" OR safety OR cost OR economic* OR "Quality of Life" OR QOL OR "quality adjusted" OR "drug efficacy"
218621

#4 (#1 AND #2 AND #3) 103
#5 (#4) 102