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

Review on TNF-alpha blocking agents in psoriatic arthritis for ZonMw

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Introduction

Psoriatic arthritis (PsA) occurs around in 11% of patients with psoriasis. (1) In the Netherlands psoriasis affects 1-2% of the general Dutch population, hence the prevalence of PsA is about 0.5%. The clinical spectrum of PsA ranges from arthralgia and enthesiopathy to a destructive and disabling joint disease. (2) The total direct costs of PsA, including hospitalizations, doctors' visits and pharmacological and non-pharmacological therapy are estimated to be $ 650 million in the United States. (3)

Disease modifying anti-rheumatic drugs (DMARDs) are the mainstay of therapy in patients with PsA. DMARDs that are effective in PsA are methotrexate (MTX), sulfasalazine and leflunomide. (4;5) As TNF-alpha plays a pivotal role in inflammation of both the skin and the synovium in PsA, several TNF-alpha blocking agents have been investigated and were subsequently registered for the treatment of PsA. Although good clinical results have been obtained, the costs of the available TNF-alpha inhibitors substantially exceed those of the traditional DMARDs. Therefore, it is debated whether the high costs of TNF-alpha inhibitors outweigh the benefits of therapy. As in rheumatoid arthritis, benefits of therapy comprise not only clinical efficacy, but also favourable effects on common comorbidities such as osteoporosis and cardiovascular disease in patients with PsA. (6) In evaluations of cost-effectiveness of therapy with TNF-alpha blocking agents, it is important to also acknowledge these potential benefits.

In this review we summarized the best evidence with respect to the major efficacy, safety and cost-effectiveness data on the four TNF-alpha blocking agents, that are currently registered for PsA treatment in the Netherlands. In addition, where available existing guidelines and protocols with respect to treatment of PsA with TNF-alpha blocking agents and data from European registries will be discussed. Available data on labour participation will be summarized. In another paragraph the costs of TNF-alpha blocking agents in therapy of PsA will be reported. As TNF-alpha blocking agents are relatively new in the treatment of PsA, there are a number of issues that presently cannot be addressed. Ongoing research in these unexplored areas will also be detailed.

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) (7) TNF-alpha blocking agents were the first biologicals to appear on the market for treatment of rheumatoid arthritis, and are still mostly used as the first biological in patient care. After rheumatoid arthritis, TNF-alpha blocking agents found their way to other rheumatic diseases such as PsA and ankylosing spondylitis. The four agents that are subject of our present report are adalimumab (Humira®), etanercept (Enbrel®), infliximab (Remicade®) and golimumab (Simponi®). As certolizumab pegol (Cimzia®) is not registered for the indication PsA, this TNF blocking agent was not discussed.

A number of randomized controlled trials (RCT) have evaluated the use of TNF-α inhibitors in PsA. A recent review reported evidence for improvement in symptoms, physical function, quality of life and radiographic progression in patients with PsA treated with TNF-alpha blocking agents demonstrating indeed that such therapy is effective and safe in patients with PsA. As a consequence several TNF-alpha blocking agents have been registered for the treatment of PsA. (7)

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
certolizumab pegol (Cimzia®)	RA, CD
golimumab (Simponi®)	AS, PsA, 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: psoriatic arthritis 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, adalumimab, 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.

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

1. psoriatic arthritis AND infliximab OR remicade
2. psoriatic arthritis AND adalimumab OR humira
3. psoriatic arthritis AND etanercept OR enbrel
4. psoriatic arthritis AND golimumab OR simponi

Selection criteria

Selection criteria that were used to include studies:

- 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 PsA
- Outcome measures include ACR20, psoriatic arthritis response criteria (PsARC) or psoriatic area and severity index (PASI)

Criteria for considering studies for inclusion

Recently published systematic reviews of RCTs and economic evaluations were included. Studies that investigated one or more TNF-blocking agents, administered with or without concomitant MTX or other DMARDs were included. The TNF-alpha blocking agents had to be administered in the recommended standard dosing regimens. Only reviews that described clinically relevant outcomes, e.g. at least ACR20 (or ACR50 or ACR70), PsARC or PASI and used study dosages that are also used in daily clinical practice, were eligible for inclusion. Additional RCTs published after the publication date of the most recently performed review for the four TNF-blocking-agents were included.

Type of studies included

Participants

Studies that included adults of 16 years or older with objectively confirmed PsA were considered with differentiation between patients who were not treated with DMARDs before and patients who had failed on DMARD therapy (mostly MTX), if possible.

Type of intervention

Studies were included if TNF-alpha blocking agents were administered alone in standard, approved doses or in combination with other active treatments compared to placebo alone or to placebo plus other active treatments. 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 mg/kg body weight every 8 weeks after an induction scheme of 0-2-6 weeks. For golimumab the, subcutaneously administered, dose is 50 mg once a month.

Outcomes

Efficacy

The primary outcomes are ACR20 improvement (ACR50 and ACR70 were considered secondary outcomes) and the PsARC and PASI. ACR20, 50 and 70 are defined as a decrease of >20%, 50% or 70% from baseline in the number of tender (n=68) and swollen (n=66) joints, plus a 20%, 50% or 70% improvement in three or more of the five following: 1) physician's global assessment of disease activity, 2) patient's global assessment of disease activity, 3) patient's assessment of arthritic pain, 4) Health Assessment Questionnaire-Disability Index (HAQ-DI), which is a validated measurement of functional status by self-reporting, and 5) serum C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). The PsARC is a response criterion adapted from the Veterans Affairs Cooperative Study of sulphasalazine. (8) The response is defined as improvement in two factors (with at least one being a joint score) with worsening of none of the following four factors: 1) patient global assessment (on a 0–5 Likert scale), 2) physician global assessment (as above) (improvement defined as decrease by at least 1 unit; worsening defined as increase by at least 1 unit) 3) tender joint score and 4) swollen joint score (improvement defined as decrease of at least 30%; worsening defined as an increase of at least 30%). The PASI incorporates the degree of erythema, induration, and scaling, as well as the area involved, in the head, trunk, and upper and lower extremity. When possible, outcomes were divided into short-term and long-term outcomes, i.e. 3-6 months and 12 months or more, respectively.

Safety

Data on serious adverse events, 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 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 active PsA. Active PsA was defined by the presence of at least 3 swollen and 3 tender joints, negative rheumatoid factor, at least 1 subset of PsA, and the presence of plaque psoriasis with a qualifying lesion at least 2 cm in diameter, (9) Age 16 years or older, and inclusion of one of the primary outcomes ACR20, PsARC or PASI. Disagreements were resolved by discussion until consensus was reached.

Results

The electronic database search resulted 1003 titles. From these, 877 publications were excluded as no patients with PsA were included or none of the four registered TNF-blocking agents was used. This first selection was based on the title and/or abstract. From the remaining 126 articles 3 systematic reviews and 5 RCTs were found eligible for inclusion. Direct comparisons between TNF-alpha blocking agents for treatment of PsA were not available, therefore the outcomes on efficacy were described per individual TNF-alpha blocking agent.

Description of included reviews and RCTs

From the three selected reviews the most recent published review of Saad et al. was included. Saad et al published a systematic review of double blind RCTs in which therapy with adalimumab, etanercept or infliximab in licensed doses in patients with PsA was compared to placebo or other active treatment. (10) In this review six RCTs were included; two on adalimumab , two on etanercept and two on infliximab. For golimumab no review was included. From the five selected RCTs only one RCT was additional to the included RCTs in the review of Saad et al. Kavanaugh et al. performed a large RCT in which therapy with golimumab was compared to standard care (or placebo) in patients with PsA. (9).

Adalimumab

Adalimumab is a humanized antibody that binds specifically to TNF-α and neutralizes its biological function by blocking its interaction with cell-surface TNF-α receptors.

Efficacy of adalimumab

We included one systematic review in which RCTs were included that compared the efficacy of adalimumab with placebo for the treatment of PsA.(10) The most frequently reported outcome in the RCTs that investigated efficacy of TNF-alpha blocking therapy in patients with PsA are the ACR20 and the PsARC. (table 2) The included patients in both studies were predominantly polyarticular or oligoarticular PsA. Saad et al. included two RCTs, encompassing 413 patients in which adalimumab was compared to placebo in patients who had an inadequate response to DMARD therapy. (11;12) In these two studies 30-50% of patients received concomitant MTX. Adalimumab was more effective than placebo for the outcome ACR20 and PsARC at 12 weeks. The pooled relative "risks" (RR, value >1 indicating improvement) for achieving an ACR20 response and PsARC were 3.42 (95%CI: 2.08-6.63) and 2.33 (95% CI: 1.80-3.01), respectively. Therefore, it is concluded that therapy with adalimumab is effective for the treatment of PsA.

Table 2. Characteristics of included RCT's in the review of Saab et al. on adalimumab for treatment of psoriatic arthritis (10)

Study	Treatment arms	Patient characteristics % concomitant MTX	Study duration (weeks)	RR for ACR 20 at wk12 (wk24)	% achieved PsARC at wk 12 (wk 24)
Mease 2005 (12)	Adalimumab (n=151) Placebo (n=162)	34 31	24	4,1* (-)	62 (60) 26 (23)
Genovese 2007 (11)	Adalimumab (n=51) Placebo (n=49)	47 47	12 (there after crossover until wk 24)l	2,4* (-)	51 (-) 24 (-)

* favors adalumimab

Safety of adalimumab

The two RCTs mentioned above also reported safety outcomes. (table 3) (11;12) Saad et al. pooled the data from these two trials and calculated RRs (RR >1 indicates more adverse events in the TNF-alpha blocking group in comparison to the control group): for withdrawal due to AE the RR was 1.98 [95%CI: 0.35-11.28]), for SAE the RR was 0.70 (95%CI: 0.25-1.94]) and for upper respiratory tract infections the RR was 0.98 (95%CI: 0.57-1.69). There were no significant differences between the occurrence of events in the adalimumab group compared to the placebo group. Since RCTs lack power to obtain statistically significant results for relatively scarce safety outcomes, it is not possible to draw firm conclusions from these data.

Table 3. Safety data of RCTs that compared adalimumab with placebo.

Study	Treatment arms	Any adverse event	Any serious Adverse event	Any infection	Any serious Infection
Mease (2005) (12)	Adalimumab (n=151) Placebo (n=162)	Not specified	5 (3,3%) 7 (4,3%)	19 (12,6%) 24 (14,8%)	Not specified
Genovese (2007) *(11)	Adalimumab (n=51) Placebo (n=49)	27 (53%) 39 (80%)	1 (2%) 2 (4%)	9 (18%) 16 (33%)	0 (0%) 1 (2%)

Until 12 weeks the study had a double blind design. After 12 weeks the study was open label.

Genovese et al. presented AEs that were reported the first 12 weeks by ≥ 5% of patients in either double blind group (placebo or adalimumab). The percentage of patients that experienced one of the following adverse events for placebo and adalimumab respectively were: upper respiratory tract infections: 8.2 vs 13.7%, injection site pain: 12.2 vs 11.8%, psoriasis aggravated: 16.3 vs 3.9%, diarrhea: 6.1 vs 2.0%, back pain: 6.1 vs 2.0%, psoriatic arthropathy aggravated 14.3 vs 2.0% and headache 6.1 vs 0%.

Etanercept

Efficacy of etanercept

Saad et al. included two RCT comprising 265 patients that compared the efficacy of etanercept with placebo for the treatment of predominantly poly-articular PsA.(10) In these two studies approximately 50% of patients received concomitant MTX. Etanercept was more effective than placebo for the outcome ACR20 (1 study, 60 patients) and PsARC (2 studies pooled, 265 patients) at 12 weeks. The relative risks (RR) for these outcomes at 12 weeks was 5.50 (95%CI: 2,15-14,04) and 2.68 (95% CI: 1.78-4.04), respectively. At 24 weeks the ACR20 response and PsARC (205 patients from one study) etanercept treatment resulted in a statistically significant better result compared to placebo: RR 3.68 (95%CI: 2.17-6.22) and 3.05 (95%CI: 2.10-4.42), respectively. (table 4)

Table 4. Characteristics of included RCT's in the review of Saad et al on etanercept for treatment of psoriatic arthritis and ACR20 response for the treatment arms. (10)

Study	Treatment arms	Patient Characteristics: % concomitant mtx	Study Duration (weeks)	RR for ACR20 response
Mease (2000) (13)	Etanercept (n=30) Placebo (n=30)	47% 47% Mean disease duration 9 yrs	12	5.50 (12 wks)*
Mease (2004) (14)	Etanercept (n=101) Placebo (n=104)	42% 41% Mean disease duration: 9 yrs	24 (therafter open label untill 48 weeks)	3.68 (24 wks)*

* favors etanercept

Safety of etanercept

The two RCTs included in the review of Saad et al. also reported data on safety. Withdrawals due to adverse events was only reported in the study of Mease et al, published in 2004. They reported one adverse event in the 101 patients of the etanercept group and one in the 104 patients of the control group (RR 1.03 95%CI: 0.07-16.24). Serious adverse events were reported in both studies. The number of serious adverse events was four of 131 in the treatment group and five of 134 patients in the control group (RR 0.86 95% CI: 0,60-13.96). Also the incidence of upper respiratory tract infections was comparable 29 of 131 in the etanercept group and 28 of 134 in the control group (RR 1.16 95%CI: 0.22-1.42). Although the number of patients years was limited, these data do suggest that the short – term safety of etanercept is not worse than placebo.

Infliximab

Efficacy of infliximab

In the review of Saad et al. studies that compared infliximab with placebo for the treatment of PsA were included also. (10) Two RCTs were included that compared infliximab 5mg/kg i.v. with placebo i.v. in patients with an active poly-articular PsA despite prior treatment with at least 1 DMARD, comprising a total of 152 patients in each treatment arm. For the 24 week trial concomitant MTX use was equally divided over the two treatment groups. In the 16 week trial of Antoni et al. MTX use was not specified. From this study we obtained a pooled RR of 5.7 (95%CI: 3.53-9.25) for the ACR20 at 14-16 weeks. The pooled RR for the PsARC and PASI50 at 14-16 weeks were 3.03 (95%CI:2.27-4.04) and 9.70 (95%CI: 4.90-19.23), respectively. Individual study characteristics are presented in table 5.

Table 5. Characteristics of included RCTs in the review of Saad et al. on infliximab for treatment of psoriatic arthritis and ACR50 response for the treatment arms (10)

Study	Treatment arms	Patient characteristics: % concomitant mtx	Study duration (weeks)	RR for ACR20 response rate (%)	% achieved PASI75 at wk16 (no. of patients assessed)
Antoni, 2005a (15)	Infliximab (n=52) Placebo (n=52)	46 65	16 (there after crossover)	6.8* (14-16 wks)	68 (n=22) 0 (-)
Antoni, 2005b (16)	Infliximab (n=100) Placebo (n=100)	47 45	24	5.3* (14-16 wks)	-

* favors infliximab

Safety of infliximab

The review of Saad et al. also reported on safety outcomes. From two studies a pooled relative risk for withdrawal for any reason and withdrawal due to an adverse event was calculated: RR 1.50 (95%CI:

0.26-8.61) and 2.90 (95%CI: 0.60-13.96), respectively. (15;16) The RR for serious adverse events was 1.35 (0.56-3.27). Since RCTs lack power to obtain statistically significant results for relatively scarce safety outcomes, it is not possible to draw firm conclusions from these data.

Golimumab

Efficacy of golimumab

Since golimumab is a relatively new TNF-blocking agent, no systematic reviews are available that included RCTs in which golimumab was compared to placebo or standard care in patients with PsA,. Kavanaugh et al. performed a large RCT in which therapy with golimumab was compared to standard care (or placebo) in patients with PsA despite therapy with disease-modifying antirheumatic drugs or nonsteroidal anti-inflammatory drugs (NSAIDs). No subgroup of patients is described in this article. (9) Concomitant MTX use was equally divided over both treatment and placebo groups. Data of individual studies are presented in table 6. The percentage that achieved ACR20 at week 14 was 9% in the placebo group compared to 51% and 45% in the groups of patients treated with golimumab 50 mg and 100 mg every four weeks, respectively. At week 24 (major secondary end point), 52% of patients in the golimumab 50 mg group (76 of 146) and 61% of patients in the golimumab 100 mg group (89 of 146) achieved an ACR20 response, compared with 12% of patients in the placebo group (14 of 113) ($P < 0.001$ for both comparisons). Consistent findings were observed for the ACR50 and ACR70 responses at weeks 14 and 24. At 24 weeks, the number of patients that achieved a PsARC response was 102 of 146 patients (70%) treated with golimumab 50 mg and 124 of 146 (85%) patients treated with golimumab 100 mg, compared to 33 of 105 patients (29%) in the placebo group. Also the PASI50 score at 24 weeks significantly improved in both groups of patients treated with golimumab compared to the placebo group. PASI50 was achieved in 76% and 82% of those treated with golimumab 50 mg and 100 mg, respectively, and in 8% in the placebo group.

Table 6. Characteristics of RCT performed by Kavanaugh et al on golimumab and ACR20 response for the treatment arms (9)

Study	Treatment arms	Patient characteristics (Active PsA)	Study duration (weeks)	% achieved ACR 20 at wk14 (wk24)	% achieved PsARC at wk 14 (wk 24)	% achieved PASI75 at wk14 (no. of patients assessed)
Kavanaugh, (2009) (9)	Golimumab 50 mg (n=146) Golimumab 100 mg (n=146) Placebo (n=113)	MTX use was stratified by baseline	14 -24	51 (52)_ 45 (61) 9 (12)	73 (70) 72 (85) 21 (29)	40 58 2,5

Safety of golimumab

At week 24, 65% (222 of 343) of the golimumab-treated patients and 59% (67 of 113) of the placebo-treated patients had experienced an adverse event. No difference in type or frequency of the adverse events was observed between the two groups. 2% (7 of 343) of the golimumab treated patients and 6% (7 of 113) of the placebo-treated patients experienced a serious adverse event. Three malignancies were reported, all occurring in the golimumab 100 mg group (2 basal cell carcinoma's and 1 prostate cancer) representing an incidence of 2.32 (95%CI: 0.48-6.78) per 100 patient-years, versus 00 (95%CI: 0.00 – 7.13) per 100 patient-years for placebo, a difference that was not statistically significant. Additional safety events reported after week 24 (including during the long-term extension after week 52 of treatment) are important to note, including 2 deaths (both in the golimumab 50 mg group) 1 due to a climbing accident and 1 resulting from small cell lung cancer.

Summary on efficacy

The results presented above indicate that therapy with these agents is more effective compared to standard therapy (placebo with or without concomitant MTX). The ACR20 outcomes of the individual studies are significantly improved in patients treated with one of the TNF-alpha blocking agents compared to controls. The efficacy of therapy might outweigh the potential increased risk for adverse events.

Summary on safety

The data presented above indicate that there is no increased risk for (serious) adverse events in patients with PsA treated with TNF-alpha blocking agents in comparison with placebo/DMARDs. 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 such as malignancies or opportunistic infections long term follow up data are necessary. However, cohort studies also have their limitations. In another paragraph of this review we will present and discuss this type of studies in more detail.

3) Clinical guidelines

Indication for TNF inhibitors and screening before starting treatment

According to the guideline of the Dutch Society for Rheumatology (NVR 2004, published ref) and a publication of Ritchlin et al., TNF blocking therapy is indicated if a patient with PsA has active disease despite adequate treatment with 25 mg/week of MTX (or the highest tolerated lower dose). (17) TNF-blocking therapy can be added, but can also replace DMARD therapy (in case of intolerance). The response and toxicity need to be reassessed.
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. (18)

4 a and b) Daily clinical practice

Data from RCTs are valuable for investigating efficacy 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 years of follow up are collected are very useful.

In addition, responses observed in RCTs can be different from the response achieved in daily clinical practice in which patients generally are older, have more co-morbidities and lower disease activity. Furthermore, in daily practice there are more variations in dosing and comedication, and there might be less compliance to treatment. A clinical practice register is of value by providing 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. We will also present data with respect to employment status.

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, in witch at the time 8,659 patients treated with anti-TNF were registered, 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.

A total of 566 patients with PsA were registered in a database of the British Society for Rheumatology Biologics Register (BSRBR). (19) In this observational study 316 patients were treated with etanercept, 162 with infliximab and 88 with adalimumab. This study, reflecting clinical practice in the UK, showed that survival of anti-TNF agents in PsA is good, with an estimated 1-year drug survival of 82%. Over a mean follow-up period of 2.3 person-years, 30.8% of patients discontinued their first anti-TNF treatment, mainly because of lack of efficacy (12.4%), (based on DAS-28 and HAQ-scores),

or adverse events (11.4%). The leading cause of drug discontinuation due to adverse events for infliximab was infusion reactions, that occurred in 7.4% of patients receiving infliximab and representing 30% of all infliximab discontinuations. A common reason for drug discontinuation for all three agents was infections. The adverse events occurred in 4.7% of patient receiving etanercept, 1.9% of patients receiving infliximab and 3.4% of the patients receiving adalimumab. Other reasons for drug discontinuation for all three agents included gastrointestinal disorders (nausea, vomiting and diarrhoea), and nervous system disorders, particularly headache.

The Finnish Society for Rheumatology has set up a national register of biological treatment (ROB-FIN). (19;20) In a cohort of patients diagnosed with PsA, treatment with biologicals for up to 2 years was examined. Of the 127 patients, 46 (36%) had discontinued their first biological drug within the first 2 years and 18 patients (14%) had been lost to follow up. Twenty patients (16%) discontinued the first biological drug due to lack of effectiveness, based on primary or secondary ACR50 response. Nineteen patients (15%) experienced an adverse event of their first biological drug within the first 2 years of treatment. The discontinued agent was infliximab in 9 patients, etanercept in 7, adalimumab in 3. Adverse events led to discontinuation of the drug in 8 cases (6%). Adverse events leading to discontinuation of the TNF inhibitor (mainly infliximab) were infusion reactions, urticaria, eczema, acute myeloid leukemia, and suspicion of multiple sclerosis. Anti-TNF-α therapy, in this study often used in combination with conventional DMARDs, appeared to have limited toxicity and persistent effectiveness up to 2 years in patients with severe peripheral PsA.(2)

Results from several national 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. (21-23) TBC 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, (21-24) No cases of tuberculosis in the BSRBR cohort in PsA patients were reported. (19)

Malignancy

Data from several national biologicals registries and long-term, open-label extension studies in patients receiving anti-TNF agents compared with the general population and with those taking traditional disease-modifying antirheumatic drugs show that there is no overall increased risk of malignancy. (19;25-27) In a Canadian cohort 665 patients diagnosed with PsA were included, 68 (10.2%) developed a malignancy at an average age of 62.4 years. The most frequently seen malignancies were breast (20.6%), lung (13.2%), and prostate (8.8%) cancer. Overall, 10.2% of patients in the Toronto PsA cohort developed cancer. There was no evidence of any difference in the cancer incidence rates when compared with the general Ontario population, both overall and by sex.

(28) 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. (19;29) Based on current literature in patients receiving anti-TNF therapy a similar pattern of malignancy as those not treated with TNF inhibitors has been observed.

Employment status in patients with PsA treated with TNF-blocking therapy

In a publication of the BSRBR data from 254 patients with PsA treated with anti-TNF-alpha were included. (26)Working status was reported at baseline and 3 years after inclusion and compared to biologic-naive rheumatoid arthritis (RA) patients. At baseline, work disability rate was 39% for PsA patients and 36% for the control group. Work disabled PsA patients were more often female (72% vs 44%, $p<0.001$), had higher baseline HAQ (2.1 vs, 1.5, $p<0.001$) and had higher baseline DAS-28 (6.1 vs 5.8, $p=0.041$) compared to working PsA patients. During 3 years of follow-up, 6.9% of patients became work disabled and 6.1% of the working disabled patients at baseline started to work again. In the RA control group these percentages were 5.1 and 3.0, respectively. No statistical analysis was conducted for these results. Kavanaugh et al. investigated the effect of infliximab therapy on employment status in PsA patients. (29) Two hundred PsA patients were randomly assigned to receive either infusions of 5 mg/kg infliximab or placebo. Employment status was assessed at baseline and after 14 weeks of therapy. In the placebo and infliximab group 66.7% and 73.0% of patients, respectively, were employed. At week 14 of the study, among patients who were not employed at baseline, 11.5% of infliximab treated patients were employed, compared to 0% in the placebo group ($p=0.084$). Among part-time employed patients, 30% in the infliximab group and 10% in the placebo group were full-time employed at week 14 ($p=0.582$). Although these result are limited to a short period of time they appear promising.

5) Quality of life and physical functioning

In 596 PsA patients registered in the BSRBR HAQ and short form (SF) 36 were assessed 6 monthly. (30) Baseline physical component scale (PCS) was 19.1, mental component scale (MCS) was 41.7 and baseline HAQ 1.88. Higher scores on the SF-36 scales indicate a better condition of the patient. PCS and MCS are both sum score scales of the physical and mental components of the SF-36, respectively. The largest changes were achieved within 6 months and remained stable thereafter. PCS improved to 29.3 at 6 and 18 months, MCS improved to 48.8 at 6 months and 48.6 at 18 months (all $p < 0.05$). Changes at 6 months were similar for etanercept, adalimumab and infliximab treated patients. HAQ improved frome 1.9 to 1.25 at 6 months and 1.38 at 18 months. The changes in SF 36 scores and HAQ, in comparison to baseline, are clinically relevant. Some RCTs addressed quality of life parameters. In the RCT of Kavanaugh et al. in which golimumab was compared to standard therapy (or placebo) the HAQ at week 24 significantly improved in the treatment group compared to the placebo group. In addition, the PCS of the SF36 improved significantly in the golimumab group.

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%).

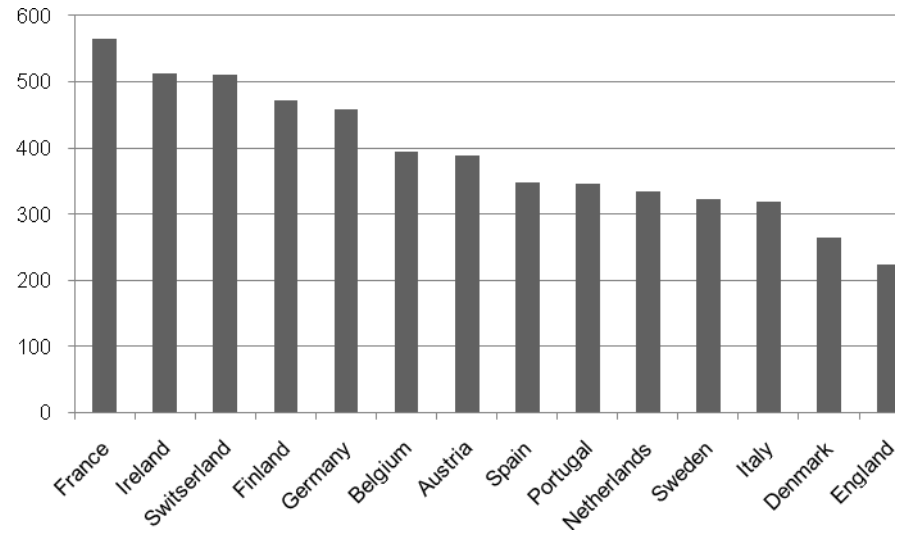


Figure 1. Pharmaceutical costs (euro's) in Europe per person per year

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. Of the recently introduced TNF inhibitors certolizumab pegol and golimumab no data are 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.

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)

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 PsA 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 organisations. Data that were not presented in Euro's were converted using the conversion rates 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.

Results

In total 13 publications were identified. Of these 13 publications, 1 recent systematic review was identified. (31) In this review all publications on cost-effectiveness of etanercept and infliximab that were published until December 2004 were included. Two additional economic evaluations were identified. (32;33)

Adalimumab

Thus far, no adequate economic evaluation on adalimumab for therapy of PsA was published.

Etanercept

We included two individual economic evaluations for etanercept in patients with PsA. (32;33) Bravo et al. published the results of a probabilistic decision analytic model in which the British Society for Rheumatology guidelines for use of TNF-alpha blocking agents were modelled. This means that therapy was only started after failure of at least two DMARDs. Use of etanercept was compared to palliative care, which is assumed to be equivalent to placebo. In the economic evaluation of Bansback et al. changes in HAQ were modelled for a cohort of patients over time.

Etanercept vs. DMARDs

Bravo et al. reported an ICER for etanercept compared to palliative care, modelled over a ten-year time horizon, for the best rebound scenario of € 30,373 per QALY gained. The ICER for a lifetime horizon was estimated to be € 19,461 per QALY gained. Bansback et al. reported an ICER per QALY gained that ranged from € 32,479 for a ten year horizon to € 76,714 for a six months horizon.

Woolacott et al. reported a range of incremental costs per QALY gained from € 17,073 (females, 40 year time horizon) to € 56,889 (males, 40 year time horizon) under the assumption that when patients fail on therapy their disability deteriorates to the same extent as it improves when they initially respond to therapy ('rebound to gain' scenario). Another scenario that the authors used is the 'rebound back to natural history' scenario. If this scenario was modelled, the incremental costs per QALY gained ranged from € 29,315 (females, 40 year time horizon) to € 56,966 (males, one year time horizon).

Etanercept vs. infliximab

Woolacot et al developed a model that evaluated the cost-effectiveness of etanercept and infliximab compared with each other. Results showed that infliximab is consistently dominated by etanercept because of its higher acquisition and administration costs without superior effectiveness.

The efficacy data used in the economic model were very limited, being derived from just three trials and 369 patients, with only 134 patients treated with etanercept and 52 treated with infliximab. Furthermore, these trial populations were not precisely representative of those for whom etanercept and infliximab are licensed: neither population was made up exclusively of patients who had failed to respond to at least two DMARDs. Other parameters within the economic model were also based on very limited evidence.

Overall conclusion

Etanercept as treatment for PsA results in increased costs but also QALYs gained. These economic evaluations are limited by the paucity of long-term data. The data available are from patients with severe disease and long disease duration. (34)

Infliximab

The only economic evaluation in which therapy with infliximab in PsA was assessed that was included in the review of Woolacot et al. was a study of Bravo et al. (the same group as Woolacot).

Infliximab vs. DMARDs

Bravo et al also presented data of an economic evaluation of infliximab for patients with PsA. They estimated an ICER for infliximab of € 42,385 per QALY gained (5-year time horizon). For a 30-year time horizon the estimated ICER was € 39,033 per QALY gained.

Golimumab

Thus far, no adequate economic evaluation on golimumab for therapy of PsA has been published.

Overall conclusion

As is the case in many economic evaluations, the assumptions applied in the models are based on limited evidence only. With respect to economic evaluations of TNF-alpha blocking agents this applies particular to the long-term withdrawal rates based on observational studies. Differences might be the result of some important methodological differences between the economic evaluations. For example, the different time frames that were used. Since 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.

9) Ongoing studies

See under 4)

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 would be very desirable to be able 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 reproduced predictive ability for response. Even when these are found, it is uncertain whether a prediction at the 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 also 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 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. (35)

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. (36-43) Furthermore, anti-drug antibodies in the presence of TNF inhibitor levels leads to the formation of immune complexes. (44) 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. (36;38;43;44) In one study in patients with Crohn's disease, higher concentrations of antibodies to infliximab predicted a higher risk of infusion reactions. (36)

Prevalence of anti-drug antibodies

In PsA and psoriasis, studies on the effect of immunogenicity on treatment response to anti-TNF therapy are limited and comprise a limited number of patients. There is only one observational cohort study describing the effect of anti-adalimumab antibodies on treatment outcome. In this study, 18% of the adalimumab treated patients developed antibodies in combination with diminishing treatment response. (45) In a phase III study 4,6% of PsA patients treated with golimumab without methotrexate developed anti-golimumab antibodies. (9) Two other, observational, studies in psoriasis patients have shown an association of anti-adalimumab or anti-infliximab antibodies and nonresponse or loss of response. (46;47) Fourty-five percent of adalimumab treated patients and 33% of infliximab treated patients developed antibodies. 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 efficacy of adalimumab and infliximab was increased. (35)

Cardiovascular disease

The excess mortality in PsA is largely due to cardiovascular disease, particularly of atherosclerotic origin such as ischemic heart disease.(48) Cardiovascular morbidity in PsA patients is also elevated by at least twofold in comparison to the general population and appears to be comparable to RA.(49) The last decades it has become widely acknowledged that inflammation plays a pivotal role throughout all stages of atherogenesis and hence the chronic inflammatory process in PsA renders our 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]). (50) Thus far similar data for psoriatic arthritis are not yet available. However, in view of the similar etiology of accelerated atherosclerotic in both RA and PsA, comparable beneficial effects of TNF-blockers on the cardiovascular risk in PsA 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 RA 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.

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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 Artritis psoriatica
"Arthritis, Psoriatic"[Mesh] OR "psoriatic arthritis"[tiab] OR "psoriasis arthritic"[tiab] OR "arthritic psoriasis"[tiab] OR "psoriasis arthropathica"[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])

#7 Search #6 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]). Result 303.

#6 Search #5 AND #4. result 337.

#5 Search #1 AND #2 AND #3

#4 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])). Result 6217769.

#3 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]. Result 1313507.

#2 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]. Result 78320.

#1 Search "Arthritis, Psoriatic"[Mesh] OR "psoriatic arthritis"[tiab] OR "psoriasis arthritic"[tiab] OR "arthritic psoriasis"[tiab] OR "psoriasis arthropathica"[tiab]. Results 4269.

EMBASE.com

#1 Artritis psoriatica
'psoriatic arthritis'/exp OR 'psoriatic arthritis':ti,ab OR 'psoriasis arthritic':ti,ab OR 'arthritic psoriasis':ti,ab OR 'psoriasis arthropathica':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

#5 #1 AND #2 AND #3 AND #4 884

#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 8,961,690

#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 1,296,205

#2 'tumor necrosis factor inhibitor'/exp OR 'infliximab'/exp OR 'adalimumab'/exp OR 'etanercept'/exp OR 'golimumab'/exp OR 'certolizumab pegol'/exp 22,656

#1 'psoriatic arthritis'/exp OR 'psoriatic arthritis':ab,ti OR 'psoriasis arthritic':ab,ti OR 'arthritic psoriasis':ab,ti OR 'psoriasis arthropathica':ab,ti 7,406

Cinahl

#1 Artritis psoriatica
(MH "Arthritis, Psoriatic") OR "psoriatic arthritis" OR "psoriasis arthritic" OR "arthritic psoriasis" OR "psoriasis arthropathica"

#2 Geneesmiddelen
(MM "Infliximab") OR (MM "Antibodies, Monoclonal") OR adalimumab OR (MM "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"

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

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 (19)

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 (175410)

S2 (MM "Infliximab") OR (MM "Antibodies, Monoclonal") OR adalimumab OR (MM "Etanercept") OR golimumab OR certolizumab OR remicade OR humira OR simponi -Search modes - Boolean/Phrase View Results (3599)

S1 (MH "Arthritis, Psoriatic") OR "psoriatic arthritis" OR "psoriasis arthritic" OR "arthritic psoriasis" OR "psoriasis arthropathica" -Search modes- Boolean/Phrase View Results (484)

Cochrane

#1 Artritis psoriatica
"Arthritis Psoriatic" OR "psoriatic arthritis" OR "psoriasis arthritic" OR "arthritic psoriasis" OR "psoriasis arthropathica"

#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"

#1 "Arthritis Psoriatic" OR "psoriatic arthritis" OR "psoriasis arthritic" OR "arthritic psoriasis" OR "psoriasis arthropathica"
209

#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
2778

#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"
218671

#4 (#1 AND #2 AND #3) 61

ZonMw t.a.v. mw Dr B. E. Vingerhoed-van Aken
Programmasecretaris

Laan van Nieuw Oost-Indië 334, 2593 CE Den Haag
Postbus 93245, 2509 AE Den Haag

Geachte mevrouw van Aken,

Bijgaand treft u de revisie van het conceptrapport Review artritis psoriatica waarin het commentaar van CVZ puntsgewijs verwerkt is. Onze respons is steeds cursief aangegeven.

Met vriendelijke groet,

mede namens de co-auteurs,

Drs. D. Jansen, apotheker

Review - Infliximab Artritis psoriatica

Indicatie:

Artritis psoriatica:
De behandeling van actieve en progressieve artritis psoriatica bij volwassenen wanneer de respons op voorafgaande therapie met DMARD's onvoldoende was.
In combinatie met methotrexaat, of alleen bij patiënten die intolerantie vertonen voor methotrexaat of bij wie methotrexaat gecontra-indiceerd is.

Respons
We hebben het review gericht op de behandeling met TNF-alfa-remmers die in combinatie met MTX of zonder MTX werden gegeven. Bij de patientkarakteristieken van de afzonderlijke RCTs wordt beschreven dat aanvullende medicatie, waaronder MTX, doorgaans gelijkwaardig over beide groepen verdeeld is. De reden waarom patiënten geen MTX gebruiken wordt in de verschillende studies niet of nauwelijks gespecificeerd, niet in de medicatie groep en ook niet in de placebo groep.

1) Farmacotherapeutische waarde

Algemeen:

-Eerdere CFH beoordelingen over TNFalpha blokkers voor de indicatie Artritis psoriatica zijn niet meegenomen in het ZonMw rapport. Verzoek om uitwerking van deze informatie, inclusief GVS beoordelingen.

Respons
Via de website " http://www.cvz.nl/publicaties/cfhrapporten/" waren voor de 4 geregistreerde middelen bij PsA de CFH rapporten beschikbaar. De geincludeerde studies in het CFH rapport komen overeen met de geincludeerde studies van dit review, de gepresenteerde resultaten komen over het algemeen dus ook overeen. Waar mogelijk hebben we ter completering onze effectiviteits en veiligheiddata aangevuld met de data uit de CFH rapporten. De conclusies over de effectiviteit en veiligheid van de betreffende middelen uit de CHF rapportages sluiten aan bij onze conclusies. Wij hebben ons beperkt tot beschrijving van de effectiviteit en veiligheid per TNF-blokker en bewust onthouden van het maken van een indirecte vergelijking tussen de TNF-blokkers, iets wat in de CFH rapportage wel wordt gedaan.

-Pagina 5 efficacy outcomes; zijn alle uitkomstmaten gevalideerde maten? Het CFH rapport betreffende infliximab dd 18 juli 2005 vermeld; voor de beoordeling van de werkzaamheid van therapeutische interventies bij artritis psoriatica zijn er geen voor de aandoening specifieke en gevalideerde criteria beschikbaar. Tevens wordt in ditzelfde rapport de Larsen-score of Sharp score vermeld voor het meten van effectiviteit. Deze scores zien we niet terug in het ZonMw rapport.

Respons
De primaire uitkomstmaten in dit rapport zijn de ACR20, PASI en PsARC. De secundaire uitkomstmaten zijn ACR50/70. Zowel de primaire als secundaire uitkomstmaten worden in dit rapport zo volledig mogelijk beschreven. In het CFH rapport wordt het volgende vermeld: "Voor de beoordeling van de werkzaamheid van therapeutische interventies bij artritis psoriatica zijn er (in

tegenstelling tot reumatoïde artritis) geen voor de aandoening specifieke en gevalideerde criteria beschikbaar". Desondanks hebben de auteurs van het CHF rapport, in overeenstemming met de literatuur, besloten om de uitkomstmaten ACR, PASI en PsARC te beschrijven, wat ook door ons gedaan is. De Larsen-score en Sharp-score zijn beide uitkomstmaten die de radiologische progressie beschrijven. Deze hebben voor de dagelijkse praktijk geen betekenis, en zijn daarom niet in ons rapport opgenomen.

-In het rapport van ZonMw wordt nergens gesproken over eventuele subgroepen van patiënten. (zie CFH rapport 18 juli 2005). Er wordt nauwelijks informatie gegeven over de patiëntkarakteristieken. Zijn de reviews wel vergelijkbaar?

Respons

Over het algemeen worden patiënten met een poly- of oligo-artritis geincludeerd, deze informatie is thans aan het rapport toegevoegd. Aangezien de CFH rapporten over het algemeen dezelfde studies hebben beoordeeld is dit vergelijkbaar.

-pag 5; er wordt een differentiatie aangegeven tussen patiënten die eerder behandeld zijn met DMARDs en gefaald hebben op deze behandeling en patiënten die niet eerder behandeld zijn met DMARDs. Deze differentiatie zien we niet terug bij de bespreking van de effectiviteit. Ditzelfde geldt voor de vermelding uitkomsten werden verdeeld over korte (3-6mnd) en lange termijns data (>12 maanden)….hier word verder niet op ingegaan.

Respons

In geen van de geincludeerde RCTs worden DMARD naieve patiënten vergeleken met patiënten die onvoldoende respons op de DMARD behandeling hebben. Op pag. 5 waarnaar gerefereerd wordt is ook aangegeven dat we dit onderscheid alleen, "if possible" zullen maken. De conclusie is dat er geen resultaten in de RCTs worden gepresenteerd waarin dit onderscheid gemaakt wordt. Naar aanleiding van bovenstaand commentaar worden thans de effectiviteitsdata in een tabel gepresenteerd met daarbij het tijdsmoment waarop is gemeten. De RCT's bevatten in het algemeen de 12 en 24 weeks data, deze data staan waar mogelijk opgenomen in dit review.

-De studies uit tabel 2, 3, 4 worden niet gerefereerd in de referentielijst. De voorafgaande behandeling van de patiënten in deze studies wordt niet vermeld.

Respons

Patiënten die geïncludeerd worden in de RCTs hebben een actieve PsA ondanks eerdere therapie met NSAIDs en/of DMARDs. De informatie over de voorafgaande therapie is, waar beschikbaar, aan het rapport toegevoegd. De verdeling van het aantal MTX gebruikers in alle RCTs, mits gerapporteerd, over de medicatie en placebo groepen was gelijk. Deze informatie is waar nodig ter verduidelijking opgenomen in het rapport. De referenties die abusievelijk niet in de tabel terecht zijn gekomen, zijn nu toegevoegd.

- Safety data van alle TNF-alpha blokkers zeer beperkt weergegeven (alleen SAE's, withdrawals en deaths). Verzoek om overzichtelijke weergave van alle bijwerkingen. (data aanvullen met safety data uit registries)

Respons

We hebben wat betreft safety data een onderscheid gemaakt tussen safety data zoals gerapporteerd in de reviews en afkomstig uit de gerandomiseerde studies en de safety data zoals gerapporteerd in publicaties gebaseerd op data van grote registries. Hierin wordt niet altijd een nadere specificatie gegeven van de adverse events. Hoewel ons rapport geen " state-of-art" systematische review is, zijn waar mogelijk, de safety data van de individuele studies in dit review opgenomen.

-Summary of efficacy pag 10; The results presented above indicate that …(placebo with or without DMARDs). Er is nergens terug te vinden wanneer wel of geen DMARDS gebruikt zijn. In tabellen wordt aangegeven dat het studies betreft TNFalpha blokkers versus placebo . (tevens…. indicatie infliximab is in combinatie met MTX!,)
Er wordt geen oordeel gegeven over de effectiviteit tussen middelen.

Respons
Er wordt bedoeld: (placebo with/or without concomitant MTX). Dit is aangepast in het rapport. Bij alle RCT's met de verschillende middelen, wordt de effectiviteit t.o.v. de placebo aangetoond. Dit is onafhankelijk van de verschillende in inclusiecriteria (zoals de gebruikte medicatie voorafgaand aan het onderzoek, alleen NSAID of ook DMARDs). Desalniettemin blijft de conclusie dat TNF-blokkersongeacht de aard van eerder (medicamenteuze) behandelingveel effectiever zijn t.o.v. van placebo. Ook in de studies met infliximab gebruikt lang niet iedereen MTX waarbij intolerantie voor methotrexaat uiteraard een belangrijk factor kan zijn.

- pag 10: -De zin "The efficacy of therapy seems to outweigh potential increase risk for adverse events." De claim is niet onderbouwd.

Respons
We zijn het eens met de reviewer dat dit niet goed is onderbouwd en dat er een voorbehoud moet worden gemaakt bij deze stelling. Wij hebben daarom de conclusie enigszins afgezwakt.

-pag 10: wat is de belangrijkste primaire uitkomstmaat? (In de tabel 2, 3 en 4 zien we alleen de RR voor ACR20 terug). Het is niet uit het rapport op te maken wat de primaire eindpunten van de RCT's waren.

Respons
De belangrijkste uitkomstmaten in dit rapport zijn de ACR20, PASI en PsARC, zie pag. 5 van dit rapport. Op grond van de huidige inzichten kan hier niet verder tussen gedifferentieerd worden. De uitkomstmaten worden in dit rapport zo volledig mogelijk beschreven. In degeincludeerde inviduele RCTs wordt doorgaans de ACR20 als primaire uitkomstmaat genomen,PsARC en PASI zijn worden veelal als secundaire uitkomstmaat gerapporteerd.

- (Summary on) safety: er wordt gesuggereerd dat bijwerkingen bij TNF alfa middelen niet verschillen van placebo. Is dat zo?

Respons
Op grond van de huidige literatuur blijkt dit inderdaad zo te zijn Het review van Saad et al. laat voor de korte termijn (+/- tot 1 jaar) geen significant verschil in (ernstige) bijwerkingen zien tussen behandeling met een anti-TNF-blokker en placebo. We merken daarbij wel op, dat het beperkte aantal patientjaren, waarover deze analyse is gedaan er toe bijdraagt dat er mogelijk (nog) geen significant verschil te zien is.

Employment status

- Het is onduidelijk in hoeverre hier sprake is van een wel of niet significante verbetering. Graag toelichten.

Respons

Voor de vergelijking uit de drie jaars follow-up en de vergelijking met de groep RA patiënten van de BSRBR data is geen statistische analyse verricht. Voor de vergelijking tussen placebo en infliximab in patienten met PsA zijn de p-waarden toegevoegd.

Quality of life

- Volgens het review is er wel significante verbetering; waarom wordt dit niet expliciet in doelmatigheid meegenomen?

Respons

Wij baseren ons op gepubliceerde doelmatigheidsonderzoeken. Als er sprake is van significante verbetering van kwaliteit van leven, dan is het aannemelijk dat dit in die onderzoeken is meegenomen. Daarom is heier geen expliciete opmerking over gemaakt

2) Kostenprognose

-Informatie over doseringen, duur gebruik, verdeling TNF alfa middelen in ziekenhuisbudget ontbreekt ook voor deze indicatie. Dit lijkt toch niet zo moeilijk om deze gegevens te verzamelen.

Respons

Uit de beschikbare bronnen, stichting farmaceutische kentallen (SFK) en (ziekenhuis)informatiesystemen kunnen helaas niet de kosten per indicatie bepaald worden. Door een gebrek aan adequate databases in de Nederland zijn dergelijke data, niet in een makkelijk analyseerbaar format beschikbaar.

-Er wordt gesproken over een eigen registry? Het is onduidelijk wat deze registratie inhoudt en in hoeverre gegevens uit deze registry voor dit review kunnen en worden gebruikt.

Respons

Uit onze praktijk blijkt dat ongeveer 20 – 30% van de 3 genoemde indicaties met biologicals behandeld wordt, ongeveer gelijkelijk verdeeld over de middelen Humira en Enbrel. Gezien de recente toetreding tot de markt van Simponi zijn het aantal patiënten die ditmiddelen gebruiken nog zeer klein. Deze getallen zijn gebaseerd op een schatting en om die reden niet opgenomen in het rapport.

3) Doelmatigheid

-Eén review en twee publicaties worden gebruikt. De review van Woolacott en de publicaties van Bravo en Bansback. In de tekst zeggen de auteurs dat deze laatste twee onderdeel zijn van de review. Dat klopt niet met de eerdere tekst en is vreemd vanwege de jaartallen, 2006, 2007 en 2006. Bij onderdeel etanercept worden de drie publicaties afzonderlijk besproken. Bij het onderdeel infliximab wordt gesteld dat Bravo onderdeel is van Woolacott. Graag verduidelijking.

Respons

Bovenstaand punt kan inderdaad tot verwarring leiden. De paragraaf over doelmatigheid van etanercept, is uitsluitend gebaseerd op de 2 individuele studies van Bravo en Bansback omdat die

meer informatie bevatten. Wat betreft de indirecte vergelijking tussen etanercept en infliximab is er wel gebruik gemaakt van de studie van Woolacot. Wij hebben de tekst hierop aangepast.

-Er wordt geen inschatting gemaakt voor de NL situatie; er wordt ook niet meer gerept over de indirecte kosten (verzuim werk) terwijl eerder in de review dit als belangrijk wordt geacht als groot voordeel van de therapie.

Respons
De Nederlandse situatie en de indirecte kosten hangen met elkaar samen. Indirecte kosten zijn heel belangrijk bij reumatische aandoeningen, maar de economische evaluaties die zijn uitgevoerd zijn in buitenlandse studies en die hebben de indirecte kosten niet meegenomen. In bijvoorbeeld in de UK bij NICE, waar in opdracht waarvan veel doelmatigheidsstudies worden uitgevoerd, worden de economische evaluaties uit vanuit het perspectief van de NHS uitgevoerd en niet vanuit het maatschappelijk perspectief waar wij in Nederland voor kiezen. Deze data zijn dus voor de Nederlandse situaties onbruikbaar en adequate Nederlandse economische analyses zijn nog niet voorhanden.

4) Doeltreffendheid

-Er zijn geen gegevens over doeltreffendheid. Er wordt niets vermeld van uitkomsten uit een eventuele eigen registry.

Respons
Wij hebben inmiddels een registry van 229 patiënten met artritis psoriatica die met etanercept of adalimumab behandeld worden. De gemiddelde follow-up is 2,17 jaar. Analyses van deze data zijn thans gaande. Een eerste indruk is dat de effectiviteit in de klinische praktijk niet essentieel verschillen ten opzichte van die gerapporteerd in de klinische trials, maar de data is nog beperkt.Gepubliceerde gegevens zijn echter nog niet voorhanden. Voor zover bekend zijn er in Nederland geen andere registries van PsA patiënten voorhanden.

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%).

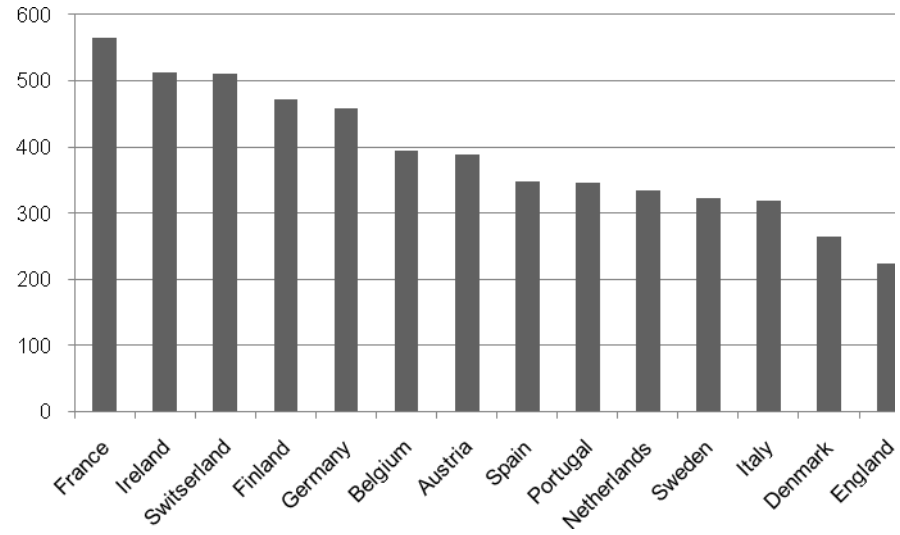


Figure 1. Pharmaceutical costs (euro's) in Europe per person per year

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.

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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