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

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

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized mainly by inflammation of joints. In Western countries approximately 1.0% of the population is affected by RA.(1) If untreated the chronic synovitis may lead to destruction of cartilage and bone, which results in joint damage, functional disability, loss of labour capacity, decreased quality of life and shortened life expectancy. There is a substantial economic impact, e.g. in the USA of $US6000-8500 per patient yearly (2;3). For the Netherlands these cost are estimated to be €5500 per patient per year. (4)

In the Netherlands approximately 145.000 persons are affected by RA. (5) The mainstay of treatment for RA is initial treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and traditional disease modifying antirheumatic drugs (DMARDs). The NSAIDs are to be lowered or discontinued when DMARDs have become effective. In this initial phase corticosteroids can be considered as bridging therapy. It is important to realize that corticosteroids are increasingly considered as DMARDs. (6) During the past decade cytokine-specific biologic therapies have become available for treatment of systemic inflammatory diseases like RA. These so-called biologicals are effective in the treatment of RA. Alone or in combination with traditional DMARDs, biologicals lead to improvement in pain and functional outcomes and to a decrease in radiological progression of joint damage. Although effective and relatively safe, TNF-alpha blocking therapy is expensive. The yearly costs of therapy with TNF-alpha blocking agents is approximately €15.000 per patient and it is subject to debate whether these costs outweigh the benefits of therapy of RA with TNF-blocking agents. It is important to realize that these benefits not only consist of clinical efficacy but also of improved quality of life and reduced work absenteeism. Furthermore, TNF-alpha blocking agents probably also have favourable effects on common co-morbidities observed in RA, particularly osteoporosis and cardiovascular disease. With respect to the increasing costs in healthcare it is naturally important to critically evaluate the necessity of certain expensive therapies.

In this review we summarized the best evidence from the literature with respect to the major efficacy, safety and cost-effectiveness data on the five TNF-alpha blocking agents, that are currently registered in the Netherlands. In addition, existing guidelines and protocols with respect to treatment of RA with TNF-alpha blocking agents are discussed. Furthermore, we give a selection of data from clinical registries in the Netherlands and other European countries, in which long term follow up of therapy with TNF-alpha blocking agents in patients with RA is performed. Certain gaps in the literature are partly filled by unpublished

data from our own registries, e.g. with respect to labour participation. Long term efficacy and safety data will also be mentioned. In another paragraph the expenses on medication in the Netherlands is 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 RA. 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 RA.

1) Summary and place in the clinical armamentarium

In rheumatology and other fields 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 RA, and are still mostly used as the first biological in patient care. The five agents that were subject of study are adalimumab (Humira®), etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®) and certolizumab (Cimzia®).

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

All five registered TNF-alpha blockers are highly effective in patients with active RA, who have inadequate responses to traditional DMARDs, as well as in DMARD-naïve patients. In early RA, combinations of traditional DMARDs including corticosteroids may be as effective as a combination containing a TNF-alpha blocker. TNF-alpha blocking agents can be prescribed as monotherapy (etanercept or adalimumab) or with concomitant MTX (all five agents). Infliximab, golimumab and certolizumab pegol are registered only in combination with MTX. TNF inhibitors can also be prescribed in combination with other DMARDs than MTX.

The major adverse events are infections, which occur at an increased rate and can in part be managed by screening and pretreatment of latent tuberculosis. Primary non-response occurs in one third of the patients, who can then be treated with biologicals with other modes of action. An important reason for secondary non-response appears to be antibody formation to the drugs, so-called immunogenicity.

The societal costs of insufficiently controlled RA justify intensive treatment and probably also expensive therapy. There are not yet enough data to conclude whether TNF-alpha blockers are effective in maintaining or regaining employment in patients with RA. Future areas of research should include among others: the profiling of patients to better predict the response to TNF blockers, the effect on cardiovascular risk, determining the optimal sequence of biologicals and evaluating the withdrawal of these drugs during sustained remission.

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: rheumatoid 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, certolizumab 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. Rheumatoid AND infliximab OR remicade
2. Rheumatoid AND adalimumab OR humira
3. Rheumatoid AND etanercept OR enbrel
4. Rheumatoid AND golimumab OR simponi
5. Rheumatoid AND certolizumab OR cimzia

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 five TNF-blocking agents
- Patients with objectively diagnosed RA
- Outcome measures include DAS and/or ACR50 (see below)

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 ACR50 (or ACR20 or ACR70) or disease activity score of 28 joints (DAS28) 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 five TNF-blocking-agents were included.

Type of studies included

Participants

Studies that included adults of 16 years or older with confirmed RA were considered. It was also tried to differentiate between patients who were not treated with DMARDs before and patients who had failed on DMARD therapy (mostly MTX).

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 3.0 – 10.0 mg/kg body weight every 8 weeks after an induction scheme of 0-2-6 weeks. For certolizumab pegol the subcutaneously administered dose is 200 mg every other week, with an induction scheme of 400mg in the first three weeks. For golimumab the subcutaneously administered dose is 50 mg once a month.

Outcomes

Efficacy

The primary outcomes are ACR50 improvement (ACR20 and ACR70 were considered secondary outcomes) and the DAS28. These are supported by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), respectively. 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 DAS28 includes the number of swollen joints, number of tender joints, a reagent of acute phase and the assessment of global health

by the patient. (8) The level of disease activity is interpreted as low (DAS28 ≤3.2), moderate (3.2< DAS28 ≤ 5.1) or high (DAS28 > 5.1). A good response is defined as a decrease in DAS28 >1.2 from baseline or a DAS 28 < 3.2. No response is defined as a decrease in DAS28 < 0.6 or a decrease > 0.6 and < 1.2 with a final DAS28 > 5.1. Any other score is regarded as moderate response. (9) We mainly focussed on DAS28 and ACR50 as outcome criteria for efficacy. 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 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 RA according to ACR criteria, 16 years of age or older, and inclusion of one of the primary outcomes ACR50 or DAS28. Disagreements were resolved by discussion until consensus was reached.

Results

The electronic database search resulted in 3021 titles. From these 3021 titles we excluded publications in which no patients with RA were included or in which none of the five TNF-blocking agents was used as treatment strategy. This first selection was based on the title and/or abstract. This resulted in 248 articles that were selected. From these 248 articles five systematic reviews and two RCTs were found eligible for inclusion. One of these was a duplicate of a study already included in the review. In the other study, a RCT to treatment with golimumab, the ACR50 results were similar to the results of the review of RCTs. (10)

Direct comparisons between TNF-alpha blocking agents for treatment of RA were not available, therefore the outcomes on efficacy were described per individual TNF-alpha blocking agent. A number of research groups have published reviews of indirect comparisons

of TNF-alpha blocking agents. Since the methodological validity of such comparisons is under debate, we did not include these indirect comparisons in the current report.

Description of included reviews and RCTs

We included one Cochrane review, which is an overview of other Cochrane reviews on efficacy and safety of available biologicals in adult patients with RA. (11) Three of the five Cochrane reviews we selected, were also included in this overview of Cochrane reviews. (12-14). The authors included all three Cochrane Reviews on biologicals for RA that had been published in the Cochrane Library up to February 2009. If a review was incomplete and/or not updated recently, the authors contacted the authors of the original review and requested data and/or an update of the review. Another included review was of Wiens et al. of the safety and efficacy of adalimumab. (15) The fifth review included was a review of the efficacy and safety of golimumab. (16) For certolizumab no Cochrane review was available. The results of the reviews are summarized below.

Adalimumab

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

The review by Singh (11) of Cochrane reviews on treatment of RA with biologicals consisted of one Cochrane review (14) in which eight trials with adalimumab were included. In five of these trials a combination of adalimumab and MTX was compared to placebo and MTX. (17-21) In one study adalimumab in combination with a not further specified DMARD was compared to placebo in combination with a not further specified DMARD. (22) In two studies adalimumab alone was compared to placebo alone. As in common daily clinical practice adalimumab is combined genrally with MTX, we focussed predomininantly on these trials. (23;24) Moreover, as ACR50 and DAS28 are the most clinically important efficacy outcomes, we focussed on these outcomes. Two of these studies included only patients with early RA, three studies included only patients with established RA and three included only patients with late RA. Early RA was defined as a duration of disease < 2 years, established RA 2 – 10 years and late RA is defined as a duration of disease of > 10 years. For adalimumab we also included the review of Wiens et al. (15)

Efficacy of adalimumab

In their systematic review of Cochrane reviews Singh et al. reported pooled data from three studies with a total of 1080 participants. The relative risk (RR) for the number of patients that reached ACR50 at 12 months for adalimumab with or without DMARD and placebo with or without DMARD was 1.88 (95%CI: 1.00–3.55). In table 2 the results of the DAS, HAQ and ACR50 response of the individual trials are presented, when available in the review of Singh et al. and in the review of Navarro Sabia et al

Table 2. Characteristics of included RCT's in the updated review of Singh et al., Navarro Sarabia et al. and Wiens et al on adalimumab and ACR50 response, HAQ and DAS28 scores for the treatment arms (11;14;15)

Study	Treatment arms	Patient characteristics	Study duration	Mean change (SD) in DAS28	Mean difference in HAQ [95% CI] at week 24.	ACR50 response rate (%) at end of FU
Bejarano, (2008) (17)	Placebo + MTX Adalimumab + MTX	Early, MTX naive	13 months			45 56
Breedveld, (2006) (18)	Placebo + MTX Adalimumab Adalimumab + MTX	Early, MTX naive	24 months			46 41 62
Furst, (2003) (22)	Placebo + DMARD Adalimumab + DMARD	Late, DMARD failure	6 months			11.3 28.9
Keystone, (2004) (19)	Placebo + MTX Adalimumab + MTX	Late, DMARD failure	12 months		-0.32 [-0.42- -0.22]	19 86
Kim, (2007) (20)	Placebo + MTX Adalimumab + MTX	Late, DMARD failure	6 months			
Miyasaka, (2008) (23)	Placebo Adalimumab	Late, DMARD failure	6 months			5 22
Van de Putte, 2003 (25)	Placebo Adalimumab (40 mg)	DMARD, refractory	3 months	-0.5 (1.1) -2.1 (2.3) (40 mg)		
Van de Putte (2004) (24)	Placebo Adalimumab	Late, DMARD failure	6 months	-0.7 (1.3) -1.7 (1.6)		8.2 22.1
Weinblatt (2003) (21)	Placebo + MTX Adalimumab + MTX	Late, DMARD failure	6 months		-0.35 [-0.56 - -0.14]	8.1 55.2

The OR of a combined ACR50 outcome at 3, 6 or 12 months for the total group was 3.70 [95%CI: 2.40 – 5.70]. The OR of the ACR20 and ACR70 improvement at these three time points were 3.09 [95% CI: 2.18 – 4.39] and 3.98 [95%CI: 2.48 – 6.4] respectively. Wiens et al. performed a meta-analysis of patients with RA. (15) The OR of adalimumab and MTX compared to placebo and MTX was calculated at 12 – 26 weeks and at 52 weeks. The OR was 3.50 [95%CI: 2.75–4.44] at 12 – 26 weeks and 2.80 [95% CI:1.16 – 6.77] after 52 weeks. In

summary, the results show that adalimumab is statistically significantly more effective than placebo.

Safety of adalimumab

The majority of studies that were included in the systematic reviews reported the following safety outcomes:

- Serious adverse events
- Serious infections
- Withdrawal due to serious adverse events
- Malignancy (mostly reported in long-term follow up studies)
- Deaths

Navarro-Sarabia et al. also reported data with respect to safety outcomes of the RCT's that were included: In the randomized clinical trial of Furst et al. in which 636 patients were included 81% in the adalimumab group and 48% in the placebo group experienced an adverse event. (22) The most frequent adverse events that were reported were respiratory tract infections, rhinitis and headache. For serious adverse events data of two studies that compared adalimumab and MTX with MTX alone were pooled. [ref Rau en ref furst]. In the study of Furst et al. 5.4% of patients in the adalimumab group versus 7.4% in the placebogroup suffered a serious adverse event. In the study of Rau et al. in both groups 5.4 patients suffered a serious adverse event. This resulting in a RR of 0.74 [95% 0.39-1.40], indication more but nog statistically significant events in the placebogroup. The most frequently encountered adverse event were upper respiratory tract infections and rhinitis. No specification of serious adverse events was presented. In table 3 the frequencies of safety outcomes from the studies are shown. Based on a total of 1987 patients in six studies the RR of serious adverse events at 12 months in those treated with adalimumab and a DMARD compared to placebo and a DMARD was 0.93 [95%CI: 0.60-1.45]. The RR for total withdrawals at 12 months when this treatment was compared to controls was 0.78 [95%CI: 0.66-0.92]. Considering the main safety outcome, i.e. withdrawals due to adverse events, the review of Navarro-Sarabia showed that patients receiving adalimumab were at significantly higher risk for this outcome compared to placebo 1.54 [95%CI: 1.12–2.12].

Table 3. Safety data from the included RCTs in the review of Navarro Sarabia et al. and updated by Singh et al. on adalimumab. (11;14)

Study	Treatment arms	Serious adverse events	Serious infections	Withdrawals due to adverse events
Furst (2003) (22)	Placebo + MTX Ada + MTX	20/270 (7%) 14/261 (5%)	6/270 (2%) 4/261 (2%)	6/270 (2%) 7/261 (3%)
Keystone (2004) (19)	Placebo + MTX Ada + MTX		1/200 (< 1%) 16/419 (4%)	13/200 (7%) 42/419 (10%)
Rau (2004) (26)	Placebo + MTX Ada + MTX	1/18 (6%) 1/18 (6%)	0/18 (0%) 0/18 (0%)	0/18 (0%) 0/18 (0%)
Weinblatt (2003) (21)	Placebo + MTX Ada + MTX			2/62 (3%) 5/209 (2%)

Etanercept

Etanercept is a recombinant human TNF-α-receptor fusion protein. It interferes with the inflammatory cascade by binding to TNF-α, thereby blocking its interaction with cell-surface receptors. One Cochrane review that was also included in the aforementioned overview of reviews of Singh et al. but was updated in 2009 included four RCTs that investigated etanercept as therapy for RA (table 4).(11;13) Etanercept with and without DMARD was compared to placebo with and without DMARD. In four of these trials a combination of etanercept and MTX was compared to a placebo and MTX. In one of these four studies etanercept was compared to placebo alone. The efficacy outcomes that were analyzed were ACR20, ACR50 and ACR70 and DAS28 scores of one study.. Two of these studies included patients with established RA and two studies included only patients with late RA.

Table 4. Characteristics of included RCT's in the Cochrane reviews of Singh et al. and Blumenauer et al. on etanercept and ACR50 response for the treatment arms (11;13)

Study	Treatment arms	Patient characteristics	Study duration	ACR50 response rate (%) at end of FU	% DAS28 remission (i.e. DAS28 <2.6 [95% CI] at 52 wks)
Moreland, (1999) (27)	Placebo Etanercept	Late, DMARD failure	6 months	5 40	
Weinblatt, (1999) (27;28)	Placebo + MTX Etanercept + MTX	Late, DMARD failure	6 months	3 39	
Emery, (2008) (29)	Placebo + MTX Etanercept + MTX	Early, MTX naive	12 months		28 [23-33] 50 [44-56]
Klareskog (2004) (30)	Placebo + MTX Etanercept + MTX	Established, DMARD failure	12 months	45 66	

Efficacy of etanercept

Considering the combined 3, 6 and 12 month outcome data, all four studies showed significantly improved ACR50 scores when etanercept was compared to placebo. In the pooled analysis, including a total of 624 patients in the treatment group and 581 patients in the placebo group, the OR was 4.97 [95%CI: 2.70-9.13]. The pooled ORs for ACR20 and ACR70 were 4.47 [95%CI: 2.70 – 7.38] and 4.05 [95%CI: 2.07 – 7.93], respectively. Emery et al. showed a statistically significant difference in DAS28 remission at 52 weeks between patients treated with etanercept and MTX compared to those treated with MTX alone. (50% versus 28%)

Safety of etanercept

Singh et al. performed a pooled analysis of a total of 1205 patients on the incidence of withdrawals due to an adverse event. The incidence of withdrawals due to adverse events was lower for those treated with etanercept and MTX compared to patients treated with placebo and MTX (OR 0.82 [95%CI: 0.56 – 1.19]). In the original review of Blumenauer et al. the following safety outcomes for the comparison of etanercept with MTX were presented: injection site reactions at 6 months of 46% in the etanercept group versus 11% in the MTX group (RR 4.4 [95% CI: 2.5 – 7.9]) and an RR 1.21 [95% CI: 0.81 – 1.79] for rhinitis at end of study (no incidences were provided): Although not statistically significant, the conclusion that etanercept was not more harmful than placebo should be interpreted cautiously. The number of patients (1205) for whom safety data are available at present may be too low to

allow definite conclusions on serious adverse events. In table 5 safety data from the individuals RCTs included in the review of Blumenauer are shown.

Table 5. Safety data from the included RCTs in the review of Blumenauer et al. and updated by Singh et al. in which etanercept was compared with control treatment. (11;13)

Study	Treatment arms	Adverse events (n/total)	Infusion site reactions (n/total)	Infection (n/total)	Rhinitis (n/total)	Malignancy (n/total)
Bathon (2000) (31)	Placebo (MTX) Etanercept	22/217 (10%) 9/208 (4%)				
Moreland (1999) (32)	Placebo Etanercept		10/80 (13%) 38/78 (49%)		9/80 (11%) 8/78 (10%)	
Weinblat (1999) (28)	Placebo Treatment		2/30 (7%) 25/59 (42%)		1/30 (3%) 8/59 (14%)	
Emery (2008) (29)	MTX Etanercept + MTX	246/268 (92%) 247/274 (90%)		8/268 (3%) 5/274 (2%)		4/268 (1%) 4/274 (1%)

Infliximab

Infliximab is a chimeric anti-TNF-alpha monoclonal antibody, which reduces the inflammation process in RA by blocking the cytokine TNF-alpha.

One Cochrane review of infliximab was included in Singh's overview of reviews. (12) In total four RCTs were included. Infliximab and a DMARD was compared to placebo and a DMARD. The doses eligible for inclusion were 1 mg/kg, 3 mg/kg, 5 mg/kg and 10 mg/kg.

Trial duration was at least 6 months. One study included patients with early and with established RA. The other two studies included only patients with established RA. The reported outcome parameters on efficacy were ACR20, ACR50 and ACR70, HAQ, SF-36 and radiographic-scores. No DAS-scores were reported. The safety outcomes were adverse events outcomes and withdrawals due to adverse events.

Table 6. Efficacy outcomes of RCTs in the review of Blumenauer et al. and updated by Singh et al. on infliximab (11;12)

Study	Treatment arms	Patient characteristics	Study duration	ACR50 response rate (%) at 14-24 wks	Mean difference in HAQ at end of study [95% CI]
Maini (1998) (33)	Placebo + MTX Infl + MTX	Established, DMARD failure	6 months	DAS28 or ACR were not used as outcome	
St. Claire(2004) (34)	Placebo + MTX Infl + MTX	Early, DMARD failure	6 months	32 46	
Maini (1999)/Lipsky (2000) (35)	Placebo + MTX Infl + MTX 3mg/kg / 8 wks 3mg/kg / 4 wks	Late, DMARD failure	12 months	8 21	 0,0 [-0.21 – 0.21] -0.20 [-0.41 – 0.01]
Quinn (2005) (36)	Placebo + MTX Infl + MTX	Early	12 months	40 80	

Efficacy of infliximab

In table 6 efficacy data of infliximab are presented. In all studies infliximab combined withMTX is compared to placebo combined with MTX. From the study of Quinn et al. it could not be retrieved whether or not patients had failed on DMARDs, the duration of diseases of the included patients was relatively short (0.7 years). The data of the other study are based on patients who had failed on prior DMARD therapy, which in the Netherlands is prerequisite before therapy with TNF-alpha inhibitors is initiated. The three studies included a total of 447 patients with RA in the infliximab and DMARD group and 372 patients with RA in the placebo and DMARD group. The ACR50 outcome at 6 and at 12 months was improved for all infliximab doses compared to control. The pooled ACR50 scores at 6 and 12 months were 6.08 [95%CI: 2.30–16.09] and 4.14 [95%CI: 2.00–8.57], respectively. This score was based on 340 patients in the infliximab group and 88 in the control group. The combined ACR50 outcomes at 3, 6 and 12 months resulted in a pooled OR of 2.92 [95%CI:1.37–6.24]. The same comparison for the ACR20 and ACR70 resulted in ORs of 2.26 [95%CI:1.21–4.21] and 3.23 [95% CI:1.42–7.37], respectively. Maini et al. also evaluated the HAQ-score at the end of follow-up. No difference in HAQ-score between infliximab and MTX and placebo and MTX was observed.

Safety of infliximab

Compared to placebo the risk for withdrawal due to adverse events was significantly higher in the group of patients treated with infliximab: 2.21 [95% CI:1.28 – 3.82]. At six months the reported incidence of infections requiring antibiotics was 31% in the infliximab group and 21% in the control group, which did not reach statistical significance. The number of patients (819) for whom safety data are available at present may be too low to allow definite conclusions on serious adverse events. From two studies that compared infliximab and MTX with placebo and MTX safety data were available. In table 7 the pooled RRs of safety are presented. (33;35) These results do not show statistically significant differences.

Table 7. Safety data from the included RCTs in the review of Blumenauer et al. and update by Singh et al. on infliximab (11;12)

Study	Treatment arms	Infections requiring antibiotics	Serious infections	Malignancy	SLE	Death
Maini (1998) (33)	Placebo + MTX Infl + MTX	3/14 (21%) 28/87 (32%)	0/14 (0%) 2/87 (2%)	0/14 (0%) 0/87 (0%)	0/14 (0%) 1/87 (1%)	0/14 (0%) 1/87 (1%)
Maini (1999) Lipsky (2000) (35)	Placebo + MTX Infl + MTX	18/86 (21%) 106/342 (31%)	5/86 (6%) 14/342 (4%)	0/86 (0%) 3/342 (1%)	0/86 (0%) 1/342 (1%)	3/86 (0%) 2/342 (1%)
Pooled RR [95% CI]		1.48 [0.99-2.23]	0.72 [0.28-1.84]	1.78 [0.09-34.05]	0.63 [0.07-5.93]	0.22 [0.05-0.99]

Golimumab

The most recent TNF-alpha blocking agent that became available is golimumab, a humanized inhibitor of TNF-alpha. By binding to both soluble and transmembrane bioactive forms of human TNF-alpha it prevents the binding of TNF-alpha to its receptors and thereby inhibits the biological activity of TNF-alpha. (37) Singh et al. also published a systematic review of RCTs in which golimumab for treatment of active RA was compared to placebo. (16) A total of four RCTs with in total 1231 patients treated with golimumab were included (table 8). (16)

Efficacy of golimumab

The groups of patients included in the study of Keystone et al. and Smolen et al. are not comparable. (38;39) In the study of Smolen et al. the majority of included patients had failed

on prior TNF therapy. This can explain the relatively small RR of therapy with golimumab compared to placebo in the study of Smolen et al. The combination of golimumab with MTX for treatment of RA was associated with significantly better efficacy than placebo for achieving ACR20/50/70 and lower DAS28 scores at 5 to 6 months follow-up. The relative risk of ACR50 of golimumab and MTX compared to placebo and MTX at 14-24 wks was 2.57 [95%CI: 1.34 – 4.94]. The DAS28 was expressed as mean difference (MD). At 4 months the MD of the DAS28 was -1.10 [95%CI: -1.69 - -0.51] in favour of golimumab compared to placebo. Remission of RA, expressed as DAS remission, had a risk difference compared to placebo of 0.10 [95%CI: 0.06–0.14] favouring golimumab. Improvement in physical function expressed as HAQ was also at 14 weeks statistically significant better in the golimumab group compared to the placebo group (MD -0.20 [95%CI: -0.25 - -0.15])

Table 8. Efficacy outcomes of included RCT's in the review of Singh et al. on golimumab (16)

Study	Treatment arms	Patient characteristics	Study duration	ACR50 response rate (%) at 14-24 wks	RR [95%CI] of DAS28 remission (RR > 1.0 favours treatment)
Smolen (1999) (39)	Placebo + MTX GLM 50 mg+ MTX	TNF failure (67%)	24 wks	29 (placebo) 38 (interventions)	1.19 [1.02 – 1.39]
Kay (2009) (40)	Placebo + MTX GLM 50 mg + MTX	MTX failure	20 wks	6 (placebo) 31 (interventions)	1.50 [0.27 – 8.43]
Keystone (2009) (38)	Placebo + MTX GLM 50 mg + MTX	MTX failure	24 wks	10 (placebo) 32 (interventions)	1.60 [1.26 – 2.01]
Emery (2009) (41)	Placebo + MTX GLM 50 mg + MTX	MTX failure	52 wks	6 (placebo) 18 (interventions)	1.81 [1.33 – 2.45]

Safety of golimumab

The most reported serious adverse events that were reported in trials in which golimumab and MTX is compared to MTX alone were infections. As shown in table 9, the risk of serious adverse events at 16-24 weeks was not higher in the golimumab group compared to the placebo group (RR1.05 [95%CI: 0.62–1.78]). Golimumab was not associated with higher risk of infections, serious infections, tuberculosis, lung infections, cancer or death. The relative risk of withdrawals due to adverse events at four months was 0.56 [0.24–1.29]) in favour of golimumab, but did not differ significantly from placebo. Obviously the patient numbers were

too small to reach statistical significance. Nevertheless, there was no suggestion that the short term risk for adverse events differed between golimumab in combination with MTX and MTX alone.

Table 9. Safety outcomes at 16-24 weeks from RCT's that were included in the review of Singh et al. on golimumab. (16)

Study	Treatment arms	Serious adverse events	Serious infections	Malignancies	Withdrawals due to adverse events
Smolen (1999) (39)	Placebo + MTX GLM 50 mg+ MTX	11/155 (7%) 8/152 (5%)	3/155 (2%) 3/152 (2%)	0/155 (0%) 1/152 (1%)	9/155 (6%) 4/152 (3%)
Kay (2009) (40)	Placebo + MTX GLM 50 mg + MTX	2/34 (6%) 4/37 (11%)	1/34 (3%) 1/37 (3%)	0/34 (0%) 0/37 (0%)	3/35 (9%) 2/35 (6%)
Keystone (2009) (38)	Placebo + MTX GLM 50 mg + MTX	3/133 (2%) 5/89 (6%)	1/133 (1%) 2/89 (2%)	1/133 (1%) 0/89 (0%)	4/133 (3%) 2/89 (2%)
Emery (2009) (41)	Placebo + MTX GLM 50 mg + MTX	11/160 (7%) 10/158 (6%)	3/160 (2%) 21/158 (123%)	2/160 (1%) 1/158 (1%)	- -
Pooled RR [95% CI]	RR > 1.0 indicates more events in golimumab group	1.05 [0.62 -1.78]	1.06 [0.40-2.86]	0.81 [0.16-4.18]	0.56 [0.24-1.29]

Certolizumab pegol

Certolizumab pegol is a PEGylated humanized Fab-monoclonal antibody that neutralizes both membrane-bound and soluble tumor necrosis factor TNF-alpha. Certolizumab has an relatively long elimination half life. Mease et al. reviewed the literature with respect to therapy with certolizumab pegol for the treatment of RA. (42) The conclusions were based on three studies: RAPID 1 (43), RAPID 2 (44;45) and the FAST4WARD trial. (45;46) The RAPID 1 and 2 studies enrolled patients with active RA despite previous MTX therapy. Certolizumab pegol 200 or 400 mg plus MTX every two weeks was compared to placebo and MTX every two weeks.

Efficacy of certolizumab pegol

The review of Mease et al. showed that at 24 weeks the improvement in DAS28 score was -2.27 (200 mg) and -2.46 (400 mg) which differed significantly from placebo (-0,5). (42) At 52 weeks the improvement in DAS28 score was -2.6 (200mg) and -2.8 (400mg) compared to -0,7 for the placebo combined with MTX group (34). The percentage of patients that improved

on the ACR50-score was also significantly higher in the groups of patients treated with certolizumab (200mg and 400mg at 24 and at 52 weeks) compared to the placebo group. In the FAST4WARD study certolizumab pegol as mono treatment showed an improve in ACR 50 of 24% compared to 4% in the placebo group, after six months treatment with 400mg every 4 weeks in patient with inadequate respons to prior DMARD treatment. This dosage is different than the registrated does of certolizumab pegol. (39;43) In table 10 the data on efficacy of certolizumab of the individual RCTs are shown.

Table 10. Characteristics of included RCT's in the review of Mease et al. on certolizumab and ACR50 response for the treatment arms (42)

Study	Treatment arms	Patient characteris-tics	Study duration	DAS28 change from baseline to end FU	ACR50 response rate (%) at end FU
Keystone (2008) (43)	Placebo + MTX CZP 200mg + MTX CZP 400mg + MTX	DMARD failure	52 wks	-0,7 -2,6 -2,8	7,6 38,0 39,9
Smolen (2009) (44)	Placebo + MTX CZP 200mg + MTX CZP 400mg + MTX	DMARD failure	24 wks	-0,5 -2,3 -2,5	3,1 32,5 33,1
Fleischman (2009) (47)	Placebo CZP 400mg	DMARD failure	24 wks	-0,6 -1,5	3,7 22,7

Safety of certolizumab pegol

The incidence of infections was 0.91 per patient year in patients treated with certolizumab Pegol (Rapid1) and 0.71 in patients treated with placebo and MTX, these infections mainly were upper and lower respiratory tract infections, urinary tract infections and herpes infections. Combination of trial data showed that the rate of serious infection adverse events was 2-3 times higher in those treated with certolizumab pegol regimens: 0.06 (overall) and 0.06 (200 mg) and 0.04 (400 mg) per patient year compared to 0.02 in the placebo group. (43;44)

Summary on efficacy

Based on our review of the literature we conclude that the effectiveness of adalimumab, etanercept, infliximab, certolizumab and golimumab is similar. Our conclusion is supported by a recent systematic literature review of Nam et al. in which the current evidence on treatment of RA with biologicals was investigated. (48) For adalimumab, etanercept,

infliximab and golimumab it is concluded that therapy of TNF-alpha blocking agents in combination with MTX is more efficacious than these TNF-alpha blocking agents alone.
Although, direct comparative data are lacking, it is assumed that the efficicay of certolizumab does not differ from the other TNF-alpha inhibitors. If MTX is not contra-indicated treatment of RA with a TNF-inhibitor in combination with MTX is preferable than treatment with a TNF-inhibitor without MTX. If MTX is contra-indicated treatment of RA with TNF-blocking agents is superior to placebo. As stated , there are no articles published in which direct comparisons of the TNF-blocking-agents are described. There are no data available on direct comparisons of TNF-alpha blocking agents with each other or with other biologicals. In their publication the "Commissie Farmaceutische Hulp" (CFH) also evaluated the efficacy and safety of TNF-blocking agents for the treatment of RA. For the recently evaluated certolizumab pegol and golimumab for the treatment of RA they based their conclusions on the same randomized clinical trials that were included in our overview. (39;40) The publication of CFH also made indirect comparisons. Although our conclusions about efficacy and safety are based on the same RCT's we decided not to make an indirect comparison, since the validity of this procedure is still under debate. (41) Therefore, the indirect comparisons which the CFH referred to were only partly included in this overview.
Efficacy outcome measures used by CFH were ACR20/50/70, DAS28 and radiological progression measured in modified Total Sharp Score (mTSS). The latter was not an outcome measure in our overview as it not used in clinical practice and therefore less relevant. The efficacy of the registered dose of golimumab was determined from 2 placebo-controlled studies, Keystone 2009 and Smolen 2009. (29,31) CFH concluded that golimumab in combination with MTX is effective for the treatment of RA in patients with active RA despite the use of DMARDs, mostly MTX. (31) They also concluded that golimumab may be effective in combination with MTX for treatment of active RA despite failure of other TNF-blocking agents. (29) CFH concluded that treatment of active RA with the registered dose of certolizumab pegol in combination with MTX is effective in case of MTX failure. The conclusions were based on the Rapid 1 and 2 study and the fast4ward study. Efficacy and safety data of these studies are also presented in our review. The conclusions drawn from the CFH publication regarding golimumab, certolizumab pegol and an earlier CFH publication for the other TNF-blocking agents for the treatment of RA were in line with the conclusions drawn in this review and therefore the earlier CFH publication on other TNF-blocking agents was not separately discussed.

Summary on safety

Given the lack of power and a relatively short duration of follow-up, RCTs are limited in their ability to adequately assess safety. However, we were able to extract data from the reviews with respect to these relatively short term safety outcomes. In general it can be stated that the risk for serious adverse events of which serious infections are the most common is not increased in patients treated with a TNF-alpha blocking agent, compared to placebo. Large observational studies addressing adverse events with adequate duration of follow-up are lacking. Longer-term data evaluating the safety of biological DMARDs have become available with their increasing use. Consequently, the majority of this long-term evidence from cohort studies is only available for infliximab, etanercept and adalimumab. These data are reported in Chapter 4, in which the daily clinical practice is discussed

3) Clinical guidelines

In The Netherlands, three clinical guidelines have been published that are relevant for TNF-blocking agents in RA:

- NVR-multidisciplinary guideline, concept 2010; Responsible Use of Biologicals. (49)
- CBO-guideline, 2009; Rheumatoid Arthritis. (6)
- NVR guideline (in cooperation with the Dutch society of physicians for pulmonary diseases and tuberculosis), 2003; Tuberculosis and TNF inhibitors. (50)

As each guideline is written for a different purpose and spectrum of health professionals, the information described in each guideline is different. However, these guidelines do not contradict each other. Below the most important aspects of these guidelines in relation to TNF-alpha blocking therapy and RA are summarized.

Indication for TNF inhibitors and screening before starting treatment

According to the draft of the multidisciplinary guideline of the Dutch Society for Rheumatology (NVR 2010, unpublished), TNF blocking therapy is indicated if a patient with RA has active disease despite adequate treatment with 25 mg/week of MTX (or the highest tolerated lower dose) and at least one other DMARD. TNF-blocking therapy can be added to but can also replace DMARD therapy. It has been shown that TNF-blocking therapy is effective in RA patients who have not previously been treated with DMARDs. (50) However, therapy with MTX is effective in 70% of the patients and is therefore still the first choice of treatment. 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. (49)

Treatment strategies in relation to TNF inhibitors, prescription and monitoring

In active RA the aim of treatment is to achieve a substantial reduction in disease activity, preferably remission. When no contraindications are present, the DMARD MTX is the first choice drug, possibly in combination with a bridging scheme with corticosteroids. In the case of persistent disease activity, rheumatoid factor or anti-CCP positivity and radiographic erosions a combination treatment should be considered after three months:

- combination of MTX + sulfazalazine + corticosteroids or
- combination of MTX + leflunomide or
- combination of MTX + sulfazalazine + hydroxychloroquin or
- combination of MTX + TNF blocking agent

Intolerance to MTX is a reason to replace it with another DMARD. In the case of failure of MTX in combination with an anti-TNF agent it can be considered to switch to a second TNF blocking agent or to switch to another biological, with a different mode of action, in combination with MTX: rituximab, abatacept, or tocilizumab (6). If prescribed in adequate doses and frequency of administration an adequate response, marked as a significant and

clinically relevant reduction in disease activity, can be expected in the majority of patients within 12-24 weeks of treatment. As concluded in Chapter 2 on efficacy there is no evidence that any of the available TNF inhibitors is more effective than the other, because direct comparisons are lacking.

The formation of antibodies (immunogenicity) against biologic agents is an important reason for decreased efficacy of TNF-alpha blocking therapy. (51) In Chapter 11 this issue of immunogenicity will be discussed in more detail. Monitoring of infections and malignancies during anti-TNF treatment is recommended, this issue is addressed in the particular safety chapters.

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 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 co-medication, and there is 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 from the Dutch DREAM registry and data from our own cohort with respect to employment status.

Safety data from registries

Infections

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, mainly within 6 months. (52;53) A high

HAQ score, older age, comorbidity and past hospitalisation predicted subsequent hospitalisation for infection. (53) From a UK registry is was concluded that there is a significantly increased risk for all serious infections during the first 90 days of therapy with biological agents compared with synthetic DMARDs. (54) No difference in infection rates between adalimumab, etanercept and infliximab was reported.

Results from several international biological registries show an increase in the incidence of TBC infection in patients treated with TNF inhibitors compared to patients with RA not treated with TNF inhibitors and compared to the general population. (55-58) Tuberculosis risk has decreased drastically with the introduction of screening measures and prophylaxis for those patients with latent TBC infection before the start of anti-TNF therapy. (55;58;59)

Malignancy

Data from several international biologicals registries and long-term, open-label extension data on adalimumab [10] and etanercept [11] show that there is no overall increased risk of malignancy. (56;60;61) Although an increased occurrence of non-melanoma skin cancer, central nervous system tumours and colorectal cancer was suggested in a Swedish cohort, the numbers were small and not statistically significant. (62) There are still concerns about the increased risk of malignancy in patients receiving anti-TNF therapy. In patients receiving anti-TNF therapy a similar pattern of malignancy as those not treated with TNF inhibitors has been observed. The risk of solid cancers is largely similar to the risk for other patients with RA. (62;63)

A recent meta analysis of observational cohort studies comparing RA patients to the general population showed the overall relative risk for malignancies in RA patients to be equivalent to that of the general population (Standardized Incidence Ratio (SIR): 1,05; 1,01 – 1,09). (63) However, lymphomas and tumours of the lung are more prevalent, whereas colorectal tumours and tumours of the breast occur less frequently (with SIRs of 2.08 (1.80 – 2.39), 1.63 (1.43 – 1.87), 0.77 (0.65 – 0.90) and 0.84 (0.79-0.90), respectively). The twofold risk of lymphomas appears to be related to disease activity, and is already present with new onset inflammatory polyarthritis. (62)

Malignancy during treatment of RA with TNF-alpha inhibitors

In an integrated database of 22 trials with etanercept (n = 4.322, 6.798 patient years) the SIR for malignancies was found to be 0.9 (0.6 – 1.3) for patients younger than 65 years old and 1.3 (0.7–1.9) for patients older than 65 .(64) This is consistent with the findings of an earlier

study with a smaller number of patient years. (65) A Swedish biological registry (ARTIS, n=6.604) and a national RA registry (n=67.743) investigated the incidence of lymphomas as compared to the general population. (66) The relative risk (RR) of RA patients with TNF-alpha blocking therapy was 2.7 (1.8-4.1) compared to the general population. No statistically significant difference in relative risk between RA patients with or without TNF-alpha blocking therapy was found (RR: 1.4 (0.8 – 2.1). A similar pattern was observed for other haematological malignancies, with an elevated SIR of 2.0, (0.2 – 7.3) found for leukaemias. (67) Presently, data of 8 European registries are being combined and analyzed, and a preliminary report shows no increase in the number of lymphomas due to anti-TNF use. (68) This finding concerning lymphomas is also consistent with the observations of the National Data Bank for Rheumatic diseases (NBD), with data from 908 rheumatology practices, who send questionnaires twice yearly to their patients. (61) Of the 19,562 patients (89,710 patientyears), 55% were treated with TNF-alpha blocking therapy, and 68% with methotrexate. The odds ratio of TNF-alpha use versus no TNF-alpha use was 1.0 (0.6-1.8) and the OR for TNF alpha plus MTX vs. MTX only was 1.1 (0.6-2.0). The SIR was 1.8 (1.5-2.2) in comparison to the general population.

Another large-scale cohort study combining an American and a Canadian cohort of RA patients, containing 1,152 biologicals-users (2,940 patient years) and 7,306 MTX users (30,300 patient years), found no significant difference between anti-TNF alpha and MTX with respect to haematological malignancies and solid tumours. (60) In contrast, in comparison to the general population, more lymphomas, myelomas, melanomas, lung tumours and tumours of the urinary tract were found.

In another study, 15,789 RA patients (40,125 patient years) were compared to 3,639 osteoarthritis patients (9,988 patient years) with respect to non-melanoma malignant skin tumours (i.e., basal cell carcinomas and squamous cell carcinomas). RA turned out to be associated with increased risk compared to osteoarthritis (HR 1,19). Use of anti-TNF-alpha without methotrexate showed an increase (HR: 1.24, p=0.089), albeit not statistically significant, while anti-TNF-alpha with methotrexate gave a doubling of the risk (HR: 1.97, p = 0.001). (69) The often-criticized meta-analysis of Bongartz et al. analysed a total of 9 trials with 3,493 anti-TNF-alpha and 1,512 placebo treated patients, and found a pooled odds ratio (anti-TNF-alpha vs. placebo) of 3.3 (1.2-9.1). (70) However, a number of methodological issues were raised with this study. (71-73) Therefore, it cannot be concluded that TNF-alpha blocking therapy leads to an increased risk of malignancies on the basis of this metaanalysis

alone. Thus far, it appears that there are no essential differences with regard to the risk for malignancies in RA between infliximab, etanercept, and adalimumab. (74)

From the above-mentioned findings the following can be concluded:Despite a twofold risk of lymphomas, the overall risk of malignancies in RA is probably not elevated compared to the general population. Pooled data of individual trials with TNF-alpha blocking agents are contradictory and donot give a definitive answer to the question of whether these agents contribute to a higher risk for development of malignancies.

It is likely that the use of TNF-alpha blocking agents in RA may lead to an increase in non melanoma skin tumours, particularly in combination with methotrexate.

It appears unlikely that the use of TNF-alpha blocking agents in RA leads to an additional increased risk of lymphomas.

Altogether, on the basis of the current data, a slightly increased risk cannot be excluded or proven. Given the very low incidence of malignancies, the impact on the individual patient is very limited.

DREAM, a large Dutch registry

The Dutch government and two pharmaceutical companies funded a multi-centre anti-TNFa register, called Dutch Rheumatoid Arthritis Monitoring (DREAM), in which RA patients who started for the first time with one of the TNF inhibitors were included. DREAM is a collaboration between 12 hospitals in the North-East of the Netherlands with the goal to improve the quality of care for patients with RA. Between 2003 and 2010 approximately 1800 patients using a biological were included.

To evaluate the effects of adalimumab, etanercept and infliximab on disease activity, functional ability and quality of life and the medication costs in a naturalistic design all patients from the DREAM register who started with a TNF inhibitor for the first time were assessed every 3 months.

Between 2003 and 2007, 916 patients were included. 707 patients had at least 1-year follow-up and full data at the time of analysis. Concerning the included patients, 267 (38%) patients started with adalimumab, 289 (41%) with etanercept and 151 (21%) with infliximab. There were significant differences between the three TNF inhibitors. Disease activity, the physical component scale of the SF36 and the use of co-medication were in favour of adalimumab and etanercept in the first year of treatment, compared to infliximab. Patients started with adalimumab and etanercept at the registered dose in 97% and 98% of the cases, respectively.

Infliximab patients, however, started in 80% of the cases with an average dose of 3 mg/kg per 8 weeks, in 18% of the cases with an average dose of 4 mg/kg per 8 weeks and 2% started with higher dosages. All patients who started with the average dose of 4 mg/kg dose did so because of local standards. It should be taken into account that these results are not based on a RCT design, so selection bias may play a role. However, a plausible explanation for the relatively low effectiveness of infliximab compared to adalimumab and etanercept is the low dose of infliximab that was prescribed in patients in the DREAM-cohort. (Kievit 2008)

A publication from the DREAM register described the adherence of rheumatologists to the Dutch guidelines for anti-TNF-alpha treatment. A total of 625 patients started anti-TNF-alpha treatment between February 2003 and January 2005; 234 on adalimumab, 254 on etanercept and 137 on infliximab. All patients completed 6 months of follow-up. According to guidelines in The Netherlands, a decrease in DAS28 of more than 1.2 within 3 months is required for continuation of the current anti-TNF-alpha agent in the treatment of patients with RA. This study used a daily clinical practice register and showed that response, defined as at least 1.2 points improvement in the DAS28 at 3 months, was not reached in 44%. According to the guidelines, those patients should have stopped treatment with anti-TNF-alpha agents. However, for most (81%) of those non-responders their anti-TNF-alpha treatment was actually continued. Interestingly, continuation despite nonresponse at 3 months seemed to have added value because 37% of the non-responders who still continued their anti-TNF-alpha agent became responders at 6 months of treatment. These patients also showed prolonged improvements in functional ability and quality of life. Obviously if the guidelines had strictly been followedi.e. cessation of the TNF-blocking agent) this delayed effect would have been missed!. The investigators recommended that if treatment is continued despite non-response at 3 months, this should only be done in patients with at least a partial response (at least 0.6 DAS28 improvement). (75)

The DREAM register authors did a systematic review of RCTs for etanercept, infliximab and adalimumab for patients with RA and compared these results with the patients included in their DREAM-cohort. The systematic literature search retrieved 12 papers, five with etanercept, two with infliximab and five with adalimumab. From the DREAM cohort 546 patients had been included in the register. Five treatment groups were observed: infliximab with MTX (n=103), etanercept with MTX (n=171) and without MTX (n=45), and adalimumab with MTX (n=186) and without MTX (n=31). For the infliximab patients, the mean time of follow-up was 20 months; for all other patients this was 13 months. The efficacy, based on ACR20, of TNF-blocking agents in RCTs exceeded the efficacy of these

drugs in clinical practice. In five of 11 comparisons there was a significant difference between the daily clinical practice data and the active drug group of the RCTs. However, in clinical practice more patients with lower disease activity were treated with TNF-blocking agents compared with those treated in RCTs. For daily practice patients who were eligible for RCTs, responses were more similar to responses reached in RCTs. Unpublished data from our own group show that the response (expressed as DAS28) to therapy with etanercept and adalimumab in daily clinical practice is comparable to the response observed in RCTs. (76)

Dose increase in DREAM

An important issue in therapy with TNF-blocking agents is whether dose increase is effective in patients who do not respond at all, or not anymore to the initial dose. A recent publication from the DREAM cohort included all patients with RA that were treated with TNF blocking therapy (adalimumab, infliximab or etanercept) and in whom the dose was increased (77). The primary objective was to determine the change in DAS28 three months after dose increase. In this cohort, 12% of adalimumab, 8% of etanercept and 36% of infliximab treated patients had their dose increased based on a decision of the rheumatologist. The maximum follow-up time was 55 months in the adalimumab patients, 96 months in the etanercept patients, and 94 months in the infliximab patients. Reasons for dose increase were non response (24%), loss of response (25.3%) and partial response (50.7%). The median time to dose increase was 10.5, 9.0 and 6.0 months for adalimumab, etanercept and infliximab treated patients, respectively. The dosage was increased from a mean of 40 mg every other week to a mean (+/- SD) of 73.9 (18.5) mg every other week in the adalimumab patients, from a mean (+/- SD) of 23.3 (4.7) mg to 36.5 (5.4) mg twice weekly in the etanercept patients, and from a mean +/- SD of 3.3 +/- 0.6 mg/kg to 5.2 +/- 1.3 mg/kg every 8 weeks in the infliximab patients. After dose increase, 13.6%, 12.5% and 7% of patients discontinued adalimumab, etanercept or infliximab treatment, respectively, within three months. Change in DAS28 at 3 months was -0.25 for adalimumab, -0.51 for etanercept and -0.22 for infliximab treated patients and only reached statistical significance for etanercept.. However, at 6 months there were no significant changes in DAS28. Mean DAS28 three months after dose increase was 4.0, 3.7 and 4.0 for adalimumab, etanercept and infliximab treated patients, respectively, which still reflected moderate disease activity.

In non-responders, disease activity improved significantly at 3 and 6 months, but only 12% reached low disease activity. In patients who previously experienced loss of response, disease activity only improved significantly at 3 months.

The authors concluded that the effectiveness of dose increase was very small or lacking for these three TNF-blocking agents. Dose increase might be effective in non-responding patients; however, disease activity remained moderate. Serum drug concentrations (and anti-drug antibodies) were not measured before dose increase in this study. This may be important as it enables distinction between primary and secondary non-responders (see Chapter 11, section on clinical impact of antidrug-antibody formation). Obviously, the effectiveness of other therapeutic options such as switching to a second TNF blocking agent or to a biological with another mechanism of action needs to be further investigated.

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

In this report we will discuss available literature on employment status and productivity.

For certoluzimab there are publications on household and work productivity: in the RAPID 1, RAPID 2 and the Fast4ward trial patients treated with certolizumab plus MTX reported less loss of productivity at home compared to the patients in the placebo group. (42) At week four the patients treated with certolizumab plus MTX also reported an average of 1.5 days missed per month compared with 2,5 days missed in the placebo group. These effects were sustained until the end of follow-up and reflected similar differences between the two groups in pain, physical function and fatigue. The latter finding may implicate that also for the other TNF-alpha blocking agents improvements in scores on pain and physical functioning scales may be accompanied by improvements in productivity.

In patients receiving Infliximab for the treatment of early RA the employability of patients was evaluated by Smolen et al. in a RCT. (Smolen 2006). Methotrexate (MTX)–naive patients with active early RA were randomly allocated to receive MTX plus placebo or MTX plus infliximab (3 mg/kg or 6 mg/kg) at weeks 0, 2, and 6 and then every 8 weeks through week 46. The change in employability was compared between patients who had a 20% response according to the ACR criteria for improvement in RA (ACR20) and those who did not have an ACR20 response and was used as major outcome measure. Among patients whose employment status changed from unemployable at baseline to employable at week 54, the percentage of ACR20 responders was greater than the percentage of ACR20 nonresponders (60% versus 18%; $P < 0.001$). Similarly, 96% of ACR20 responders retained their employable status from baseline through week 54, compared with 77% of ACR20 non-responders ($P < 0.001$). Comparable trends were observed when the data were categorized by treatment group. (Smolen 2006) The actual employment rates among patients in the 2 treatment groups were not different. However, patients with early RA who were treated with MTX plus infliximab had a higher probability of maintaining their employability compared with those who were treated with MTX alone. Given the short-term nature of the study and because of the subjective, patient-reported data these must be interpreted with caution.

Data from the Stockholm anti-TNFa follow-up registry (STURE) were studied in a observational study by Augustson et al. (78) Patients with RA (n=594) aged 18–55 years, (mean (SD) 40 (9) years) followed for up to 5 years were included with hours worked/week as

the main outcome measure. In all (total of 594 included patients), 66% of patients were female, and infliximab was the most common drug used (52.9%) followed by etanercept (34.5%) and adalimumab (12.6%). There were no between-drug differences, except for HAQ at baseline, most likely reflecting the later market introduction of adalimumab when an intention to treat earlier had developed. At baseline the average patient worked half time, but during the first year of treatment this was increased by approximately 4 hours per week. After the first year smaller annual improvements occurred. The shape of the trajectory was similar to the development in measures of disease activity, physical function and pain, although these measures had a more rapid improvement and had reached a more pronounced plateau at 1 year. Assuming that the patients' ability to work had remained unchanged over 5 years without biological treatment, the indirect cost gains from improved ability to work in continuers would offset approximately 40% of the drug cost. Data were not specified for separate drugs, therefore no comparison can be made between the drugs infliximab, adalumimab and etanercept. The major limitation of the study is that there was no control group to which the ability to work changes could be compared to assess what would have happened without treatment. Although RA is a progressive disease and ability to work in patients with RA has been shown to be characterized by deteriorating ability to work over time this study could demonstrate increases in hours worked.

The authors conclusion was that the data from the population-based registry indicate that biological therapy is associated with increases in workforce participation in a group typically expected to experience progressively deteriorating ability to work. This could result in significant indirect cost benefits to society. The results from this study based on STURE data (reflecting the Swedish population and social infra-structure) are concordant with some previous studies on effects on ability to work of anti-TNF treatment.

Due to the lack of Dutch registry data, we analyzed data from our own, observational cohorts of patients with RA treated with either adalimumab or etanercept. At baseline and every year thereafter, patients completed a questionnaire about their working status. Presently, one year data are available for 210 patients treated with adalimumab and 213 patients treated with etanercept. At baseline, 82 (38,5%)_of the 213 patients treated with etanercept had a job; they worked an average of 27.2 hours per week (SD 12.0, range 4-65 hours). In the group of patients treated with adalimumab, 82 (39.2%) of the 210 patients had a job and worked an average of 26.1 hours per week (SD 12.4, range 3-60 hours). During the first year of

etanercept or adalimumab treatment 21 and 20 patients, respectively, quitted their jobs and 10 patients in both cohorts started to work. After one year of treatment the average number of working hours was 26.5 and 28.3 per week in the etanercept and adalimumab cohort, respectively. These numbers did not significantly differ from baseline. The reported reasons for quitting job were: disease related reasons (20%), retirement (40%), starting education (10%), household activities (20%), other reasons (20%). In a systematic review in progress (unpublished data) by our colleagues from VU Medical Center and Maastricht University of that assessed the effect of biologicals on work participation (absenteeism, presenteeism and employment status) in 19 articles, it was observed that all cohort and RCT studies showed positive results on both absenteeism and presenteeism. (79) However, the effect on employment status was more conflicting. Conclusions have to be drawn with caution due to high heterogeneity in used outcome measures, study populations and study designs.

5) Quality of life and physical functioning

Since TNF-alpha blocking agents reduce signs and symptoms and inhibit progression of structural damage, low disease activity and remission have now become goals of therapy. These goals are not only achievable, but can also be maintained over several years. Importantly, biologicals also improve patient-reported quality of life such as the SF-36 and health related quality of life (HRQoL)

Clinical trials have shown that etanercept, infliximab and adalimumab in combination with MTX improve a variety of HRQoL measures compared with MTX alone. (80) In a study in which etanercept plus MTX was compared with placebo plus MTX, more patients achieved normal physical function after 52 weeks of treatment (based on a normal population-based HAQ-DI score of 0.49 or less (55% vs 39%, p<0.0004)) (29). In addition, after 52 weeks, the pain VAS changed -41.9 for etanercept treated patients, versus -31.4 for MTX only treated patient. (80) St. Clair et al found that patients receiving infliximab plus MTX also reported statistically significant improvements in physical functioning after 1 year compared with those receiving placebo and MTX, (76% of IFX and MTX patients achieved an improvement in HAQ of at least 0.22 (considered clinically meaningful) in comparison to baseline vs. 65% in the MTX and placebo group). (34) The SF-36 scores of the infliximab treated group also improved significantly more in than the MTX only treated group (median increases of 11.8 vs 8.9, p=0.003 for the Physical Component Summary score). (34) After 2 years of treatment with adalimumab plus MTX 72 patients reported meaningful improvement in physical function (delta HAQ > 0.22) compared to those treated with MTX alone. (18) Kimel et al found that the physical health of patients treated with adalimumab and MTX was similar to the US general population after 52 weeks (SF36 Physical Component summary of 47.5 vs 48.3; p=0.25), but this was not found for MTX monotherapy (44.2 vs 48.3; p < 0.001). (81) From the review of Singh et al. of golimumab it is concluded that golimumab improves also function and quality of life. (16) The mean decrease in HAQ from baseline to 14 weeks was 0.20 (0.15-0.25) lower in the golimumab treated group in comparison to the placebo treated group. In addition, the same review demonstrated that almost twice (1.8) as many golimumab treated patients achieved the HAQ minimal clinically important difference (decrease of ≥ 0.22) compared to the placebo treated patients. (16) It has been shown that certolizumab in monotherapy and in combination with MTX, significantly improves several aspects of HRQoL in patients with long-term RA. The HAQ of these patients for example decreased 0.5 for certolizumab (at both 200 and 400 mg dose) at 24 weeks versus 0.14 for placebo treated

patients. (80) Patients treated with certolizumab pegol also reported significant and clinically meaningful reductions in fatigue at 24 weeks (-1.69 on the fatigue assessment scale (FAS); vs. -0.27 for placebo treated patients) and pain (Pain VAS change from baseline -20.6 vs 1.7).

For adalimumab and etanercept we have unpublished cohort data regarding quality of life related outcomes. HAQ and SF-36 scores were available at baseline and one year thereafter for 155 and 159 patients, respectively, in the adalimumab cohort and for 163 and 143 patients, respectively, in the etanercept cohort. Baseline HAQ score for etanercept and adalimumab treated patients was 1.20 (SD 0.67) and 1.23 (SD 0.67) respectively. After one year of treatment the HAQ score improved significantly in both the etanercept and the adalimumab cohort: 0.83 (SD 0.63) and 0.77 (SD 0.68). All 8 SF-36 scales improved significantly in both cohorts and this improvement was comparable in both cohorts. Clinically relevant improvement (82) was achieved in the following scales: physical functioning and pain (minimal improvement), the role of limitations due to emotional problems (moderate improvement) and the role of limitations due to physical health (large improvement).

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 expensive drugs). The level of drug spending per resident did not change compared to 2007. In the surrounding countries the drug expenditure per resident is, on average,18% to 68% higher than in the Netherlands (Belgium (€ 395), Germany (€ 458) and France (€ 564)). Due to increased use of expensive drugs, in some countries 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%).

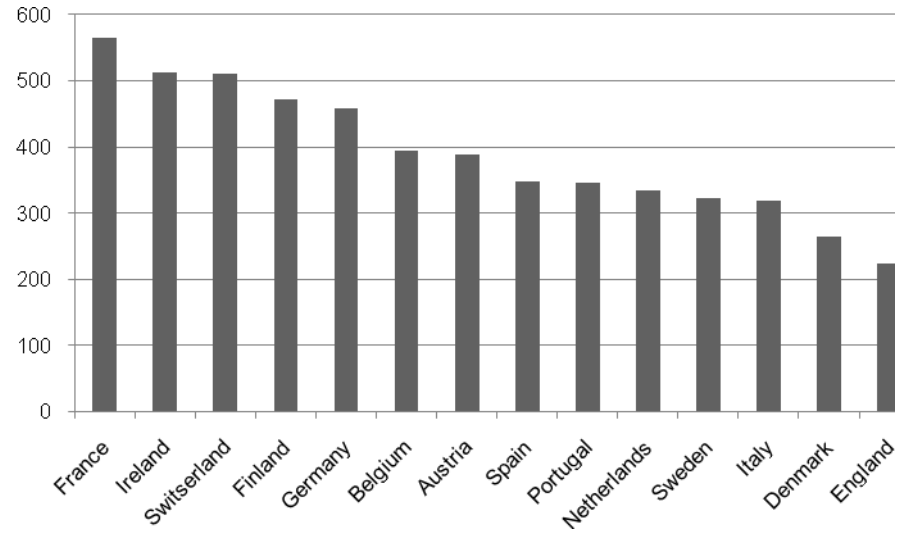

Figure 1. Pharmaceutical costs (euro's) in Europe per person per year

Drug expenditure, covered by healthcare insurance, provided by Dutch pharmacies in 2009 was € 4.789 million. This is € 47 million (1%) higher than the spending on drugs 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 the costs of a prescription exceeded €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 juni 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. Despite the effort, comparisons of the expenditure of TNF blockers to other European countries is unfortunately not readily available.

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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 it 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 costs of the anti-TNF medication based on the registrated dosage for the treatment of one RA patient per year are € 14.965,64 for Humira, € 14.970,81 for Enbrel, € 14.965,62 for Simponi and € 15.270,43 for Cimzia. Cimzia is the only drug with a start dosage, with an

additional costs of € 1.755,60. These prices are medication costs including tax, additional fees for the distribution by a pharmacy are not included*.

*Bron: http://www.medicijnkosten.nl/default.asp

Table: Top 10 of pharmaceutical expenditures in the Netherlands 2009

	Generic name (listing 2008)	Brand name	Indication	expenditure in milion € †
1	Adalimumab (5)	Humira	Rheumatoid arthritis	148 (+37%)
2	Atorvastatine (1)	Lipitor	Lipid lowering	146 (-12%)
3	Etanercept (4)	Enbrel	Rheumatoid arthritis	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 (http://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

To inform policy makers regarding reimbursement of interventions for RA through the public health insurance system, and to inform clinicians, it is important to gain insight into the cost-effectiveness of various treatment options for RA. In this chapter we summarize the results of recently published systematic reviews of economic evaluations of the five TNF-alpha blocking agents. These studies were updated, if necessary, with additional cost-effectiveness analyses. We used original studies if no review was identified.

Methods

A systematic search was performed to retrieve all published systematic reviews of health economic evaluations and cost-effectiveness analyses of treatment of RA in which at least one of the five 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.

Outcomes

We retrieved incremental cost effectiveness ratio's (ICER), which reflect the additional 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 69 publications were identified. Of these 69 publications, one recent systematic review was identified. (83) In this review all publications on cost-effectiveness of adalimumab, etanercept and infliximab that were published until December 2008 were included. Two additional economic evaluations were identified (84;85) as well as two reports of the National Institute for Health and Clinical Excellence (NICE), UK, on golimumab and certolizumab. (www.nice.org.uk)

Adalumimab

Below, the results from a recently published systematic review of economic evaluations from a societal point of view of several treatment options with adalimumab in RA are summarized.

(83) If information in the publication of this review of Schoels et al. was lacking or not clear we retrieved data from the original publications.

Adalimumab (monotherapy) vs. DMARDs

For the comparison of adalimumab versus DMARDs there is only one thorough analysis available from Bansback et al. (86) This study reported an ICER for adalimumab as monotherapy versus DMARD of €41.561 per QALY. These results were based on a lifetime model. Other less thorough analyses also reported ICERs per QALY for the same patients (DMARD failure) and outcome (ACR50) for adalimumab as monotherapy compared to DMARDs. For patients who had failed on a DMARD and were treated with adalimumab as monotherapy Brennan et al. reported an ICER of € 26.823 per QALY. (87) Also Chen et al. published results on the comparison of adalimumab as monotherapy versus DMARDs. For DMARD-naïve patients an ICER of € 61.066 per QALY was calculated. (88) For patients who had failed on DMARD therapy an ICER of € 46,088 per QALY was calculated. It was not clear whether in this study of Chen et al. ACR20, ACR50 or ACR70 was used as outcome.

Adalumimab plus DMARDs (MTX) vs. DMARDs (+ placebo)

In the aforementioned study of Bansback et al. the ICER of adalimumab combined with MTX versus DMARDs in patients that had failed on previous DMARDs was €34.167 per QALY, per improved patient according to the ACR50 or per achieved good DAS28. These results were based on a lifetime model. Brennan et al. for the same patients (DMARD failure) and outcome (ACR50) reported an ICER of € 31,237 per QALY for adalimumab with MTX compared to DMARDs. (87) Chen et al. reported for the comparison of adalimumab and MTX versus MTX an ICER of € 197,027 per QALY for DMARD naïve patients and an ICER of € 34,566 per QALY for patients that had failed on DMARD therapy.(88)

Overall conclusion

The results summarized above indicate that the incremental costs per QALY for adalimumab do not exceed €41.561. It has to be realized that these calculations are based on only direct costs. Since TNF-alpha blocking agents are effective it is reasonable to assume that when also indirect costs of productivity loss are incorporated in the economic evaluations the incremental costs of TNF-alpha blocking therapy compared to traditional DMARD therapy in patients with established RA might be lower.

Etanercept

Etanercept vs. DMARDs

In their thorough economic evaluation Bansback et al. reported an ICER of € 36,927 per QALY for etanercept as monotherapy compared with a DMARD per improved patient according to the ACR50 or per achieved good DAS28. (86)

Etanercept plus DMARDs (MTX) vs. DMARDs (+ placebo)

Bansback et al. calculated an ICER of etanercept combined with MTX of € 35,760 per QALY compared to a DMARD alone. (86) Schoels et al. in their review of cost-effectiveness analyses reported incremental costs per QALY that ranged from € 27,652 to € 46,494 for the comparison of etanercept plus a DMARD (mostly MTX) versus a DMARD alone. (83)

Overall conclusion

The economic evaluation of the cost-effectiveness of etanercept shows that the incremental costs per QALY do not exceed € 46,494. Also in these calculations the indirect costs are not incorporated in the model. It is possible that when loss of productivity is taken into account therapy with etanercept will be more beneficial from a cost-effectiveness point of view.

Infliximab

Schoels et al. identified in total 14 CEAs. (83) Of these there where 9 in which infliximab was compared to DMARDs.

Infliximab vs. DMARDs

Since monotherapy with infliximab is uncommon, there are very few publications of economic evaluations that calculated an ICER for the comparison of infliximab as monotherapy. In a cost-effectiveness analysis of Brennan et al. for the comparison of infliximab as monotherapy versus DMARDs in patients in whom DMARD therapy had failed an ICER of 26,823 per QALY was calculated. (87)

Infliximab plus DMARDs (MTX) vs. DMARDs (+ placebo)

Most ICERs were calculated in patients who had failed on one DMARD and were treated with infliximab plus MTX. Bansback et al. calculated an ICER for the comparison of infliximab plus MTX with a DMARD of € 48,333 per QALY gained. (86) In other economic

evaluations (N=5) that were included in the review of Schoels et al. the ICER per QALY gained for this comparison ranged from €16,100 to € 21,656 compared to a DMARD. (83)
Van den Hout et al. concluded from their economic evaluation that combination therapy of infliximab and MTX in patients with recent onset RA results in significant improvement in QALYs. (84)They calculated a probability at which willingness to pay combination therapy of infliximab and MTX is cost-effective compared to other strategies. Below €20,000 per QALY combination therapy with prednisone has a higher probability to be cost-effective. In addition, whether combination therapy with infliximab is cost-effective depends on the extent to which productivity is valued. The authors state that infliximab costs could be compensated for by savings on productivity. (84)

Overall conclusion

The cost-effectiveness analysis of infliximab shows that the incremental costs per QALY do not exceed € 48,333 for the most common indication and strategy of infliximab (infliximab plus MTX in patients who had failed on a DMARD). Also in these calculations the indirect costs are not incorporated in the model. It is possible that when loss of productivity is taken into account therapy with infliximab will be more beneficial from a cost-effectiveness point of view.

Golimumab

This paragraph considers cost-effectiveness of golimumab based on a recent report of the National Insitute for Health and Clinical Excellence (NICE), UK (2010). The manufacturer submitted two decision-analytic Markov models to NICE, each with a life time horizon. Both models evaluated golimumab as part of a sequence of treatments. One model compared golimumab in a DMARD-experienced population with TNF inhibitors and MTX in patients with an inadequate response to two DMARDs. The other model compared golimumab in a TNF inhibitor-experienced population with rituximab plus MTX in patients with an inadequate response to two DMARDs and a TNF inhibitor. All treatments were given in combination with MTX. MTX monotherapy was included as a comparator in each model.

Golimumab vs. DMARDS

The estimates of cost effectiveness for golimumab and the other TNF inhibitors for patients who had previously received conventional DMARDs ranged from € 23,044 to € 28,805 per QALY gained in comparison with MTX. For the group of patients who had had previous

treatment with both conventional DMARDs and a TNF-blocking agent and for whom rituximab is contraindicated or withdrawn because of an adverse event, the ICER for golimumab in comparison with MTX was € 32,261 per QALY gained. However, the NICE committee was concerned that these ICERs were likely to be underestimates.

Overall conclusion

The NICE committee has published draft recommendations based on evidence submitted by the manufacturer and consultation of clinical specialists and patient experts. The Committee does not recommend golimumab as a treatment option for RA in patients who have had therapy with conventional DMARDs only and in people who have had therapy with a TNF-alpha blocking agent and for whom rituximab is appropriate. The Committee does not recommend golimumab as a treatment option for RA in patients who have had therapy with a TNF-alpha blocking agent and for whom rituximab is contraindicated or is withdrawn because of an adverse event.

The NICE committee that evaluated the economic models concluded that some important information for determining cost-effectiveness was missing, for example, ACR70 response data, rates of disease progression while on treatment, and the indirect methods for deriving estimates of utility. The final recommendations are expected within a few months. In the UK additional conditions have to be fulfilled before biologicals can be prescribed/reimbursed. Since in the Netherlands these conditions are less stringent and from a scientific point of view there are no reasons to assume a different efficacy/safety profile when golimumab is compared to the other TNF-blocking agents, we feel that the NICE (preliminary) recommendation should not be applied in the Netherlands. A definite decision or recommendation concerning golimumab cannot be made at this point in time.

Certolizumab

This paragraph considers cost-effectiveness of certolizumab pegol in the treatment of patients with moderate to severe RA who have had an inadequate response to DMARDs, including MTX. This paragraph is a summary of the Evidence Review Group Report, a collaboration of the Universities of Birmingham and Leeds, commissioned by the NIHR HTA Programme on behalf of the National Insitute for Health and Clinical Excellence (NICE), UK. (89) Certolizumab was considered as monotherapy or as combination therapy with MTX. For combination therapy in the economic analysis four comparators were considered: etanercept, infliximab, adalimumab and rituximab; for monotherapy economic analysis there were two

comparators, adalimumab and etanercept. Two scenarios were adopted for the cost-effectiveness analyses; one scenario included a patient access scheme for certolizumab in which patients received the first ten syringes of certolizumab treatment at no cost to the NHS and in the other scenario there was no patients access scheme.

Certolizumab vs. other biologicals

Results showed that certolizumab dominated adalimumab, which means that mean costs of certolizumab were lower and effects on QALYs larger, because the incremental costs were €-2,352) and the incremental effects 0.215 QALYs. The ICER compared with etanercept was €31,582 per QALY gained; etanercept was more costly than certolizumab (incremental costs €-4,092) and more effective (incremental effects -0.13 QALYs).

Certolizumab plus MTX vs. other biologicals

Certolizumab plus MTX dominated etanercept plus MTX, adalimumab plus MTX and infliximab plus MTX. The ICER compared with rituximab plus MTX was € 9,072 per QALY The incremental costs were € 2,643 and incremental effects 0.292 QALYs.

Overall conclusion

Although the model supplied by the manufacturers concluded that certolizumab is cost-effective compared to other biologicals, the Evidence Review Group made some critical comments. The economic model was internally consistent and robust, and clinical and cost data used to populate the model were taken from appropriate sources. However, there were also some major limitations related to inadequate selection of the study population, the use of indirect comparison meta-analysis, inconsistent inclusion of data, insufficient consideration of heterogeneity among studies included in the economic model, uncertainty in the validity of data on quality of life and utilities, and exclusion of costs associated with adverse events. The Evidence Review Group suggested that the effectiveness data used in the economic model are likely to overestimate the clinical effectiveness of certolizumab. Also, the revised economic model included some unexplained deviations from the originally submitted model. The NICE committee concluded that certolizumab pegol could be considered a cost-effective option for the treatment of RA if used in the same way as other TNF inhibitors (NICE TA186, 2010).

9) Ongoing studies

European registries

There are a number of European registries that monitor current clinical practice. Soderling et al. described a Swedish register of biological treatment in patients with RA in southern Sweden. (90) This so called *South Swedish Arthritis Treatment Group* (SSATG)-register is a register that covers more than 90% of all prescriptions of biologics for RA. During 1999-2006 a total of 1839 patients with RA and 2704 treatment occasions were recorded. Trends over time show that the duration of disease before start of therapy with biologicals is decreasing in that period, from almost 14 years to less than 10 years indicating that therapy with TNF-alpha blocking agents is initiated earlier. Also a decrease in mean baseline DAS28 and baseline HAQ over time between 1999-2006 were observed, although the DAS28 remained high.

In a Danish registry called DANBIO, data were analyzed from a cohort of patients with RA who started with biologicals for the first time between 2000 and 2005. (91) For each calendar year a cohort was identified, which resulted in a total of 1813 patients. The characteristics of the patients in the five cohorts were compared. DAS28 for each cohort was determined at start of therapy and at 12 months follow-up. A significant improvement in treatment response to TNF-blocking agents was seen over the years, despite a decreasing baseline disease activity levels. The number of patients that used concomitant DMARD therapy decreased from 2000 to 2005. The use of prednisone and MTX decreased from 66-41% and 81-71%, respectively. The median dosage of MTX nearly doubled from 12,5 to 20 mg weekly in this period. The improved treatment response despite decreasing baseline disease activity levels was remarkable since these baseline disease activity levels were lower compared to the disease activity of patients that were included in RCTs. Therefore the authors emphasise the need for observational studies of efficacy in addition to these RCTs. In chapter 4 data from European registries with respect to safety are already discussed.

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, there has not been much support for such trials from the involved companies.
3. Evaluation of the optimal sequence of biologics. This could be performed within rheumatology networks.
4. Effect of stopping or dose decrease of TNF blockers in case of sustained remission. This could also be performed within rheumatology networks.
5. More data on work participation and productivity in RA patients receiving anti-TNF-alpha treatment are needed in different stages of the disease.

11) Research into unexplored areas

Immunogenicity of TNF inhibitors

Biologicals that block TNF are powerful modalities in the treatment of RA, however, both chimeric and human biologicals can induce neutralizing 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.

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.(51;92-96) Furthermore, anti-drug antibodies in the presence of TNF inhibitor levels leads to the formation of immune complexes. (97) 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. (51;92;94;97) In one study in patients with Crohn's disease, higher concentrations of antibodies to infliximab predicted a higher risk of infusion reactions. (94)

Prevalence of anti-drug antibodies

In RA there are several studies, mostly observational cohort studies, in anti-TNF treated patients where the effect of immunogenicity against these biologicals is shown: in infliximab treated patients, anti-infliximab antibodies are present in 8-52% of patients; (33;35;51;92;93) in adalimumab treated patients, anti-adalimumab antibodies are present in 4,9-87% of patients; (23;24;95;98;99) in golimumab treated patients from a phase III trial, anti-golimumab antibodies are present in 2,1% (in psoriatic arthritis patients antibodies were present in 4.6%); (38);(100) in certolizumab pegol treated patients from a phase II trial, anti-certolizumab antibodies were detected after a second infusion, the incidence varied with the

dose and was lower in higher dose groups. (101;102) Anti-certolizumab antibodies were also detected in Crohn's disease patients treated with certolizumab pegol.(32)

Adalimumab, infliximab, golimumab and certolizumab pegol are (parts of) immunoglobulins. The structure of etanercept is different, it is a genetic fusion of recombinant soluble TNF receptor and the Fc portion of human IgG. Due to its structure, it is not known what role immunogenicity has in etanercept treatment. Antibodies against etanercept are detected in only 0-5,6% of patients.(28;103;104) These antibodies appeared to be non-neutralizing and therefore the clinical relevance of these antibodies is questionable.

Clinical impact of antidrug-antibody formation

Two recently published studies showed that the presence or absence of anti-drug antibodies to the first TNF inhibitor plays an important role in the response to the second TNF inhibitor.(105;106) In addition, patients who developed antibodies to their first TNF inhibitor are more likely to develop antibodies to there second TNF inhibitor.

Patients treated with infliximab who fail to respond can be divided into patients that did or did not develop anti-infliximab antibodies. When these patients switch to a second TNF inhibitor, adalimumab, patients who did not develop anti-infliximab antibodies responded significantly worse compared to TNF naive patients and patients that did develop anti-infliximab antibodies. (ΔDAS28 after 28 weeks of adalimumab treatment: 0.9, 1.7 and 1.2, respectively). Anti-infliximab positive patients developed significantly more often anti-adalimumab antibodies compared to TNF naive patients.

Patients treated with adalimumab or infliximab who developed anti-drug antibodies responded comparably to etanercept as did TNF naive patients, however, patients who did not develop antibodies to their first TNF inhibitor and failed to respond, responded significantly worse (delta DAS28 after 28 weeks of etanercept treatment: 2.0, 2.1 and 2.1 respectively).

Cardiovascular disease

The excess mortality in RA is largely due to cardiovascular disease, particularly of atherosclerotic origin such as ischemic heart disease. Cardiovascular morbidity in RA patients is also elevated by at least twofold in comparison to the general population. 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 RA 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. Very recently 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]). (107) Our own data in a prospective cohort of 400 patients either receiving etanercept or adalimumab indicated a 30% risk reduction of cardiovascular disease in comparison to a cohort of RA patients not treated with TNF-blockers.(108;109) Although DMARDs, particularly MTX, also decrease the cardiovascular risk in RA, the risk reduction with TNF-blockers appears to be much larger. Whether this implicates the necessity of more/earlier anti-TNF use will be the subject of future studies.

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 executed by hospital pharmacies for the intravenously administered infliximab, and by nationally operating specialized pharmacies, with a separate company for each of the other, subcutaneously administered TNF blockers. There are a few exceptions including the *Maartenskliniek,* a specialized hospital for musculoskeletal diseases, that distributes subcutaneous drugs on its own, and some local pharmacies that provide for individual patients. Should these drugs become financed through the hospital budget, as is foreseen for mid-2011, the hospitals will become responsible for the distribution, which may lead to other distribution modalities.
In a letter to the health minister dated July 20, 2010, the *Nederlandse Vereniging van Ziekenhuisapothekers* (NVZA) and the *Nederlandse Vereniging voor Poliklinische Farmacie*

(NVPF) have stated that they are prepared to actively contribute to the efficient use of TNF blockers without relevant consequences for the availability of these drugs, and that they support the idea of putting the control and the accountability for the costs in the hands of the hospitals. Furthermore, these pharmacist societies as well as the NVR have voiced grave concerns about the availability of TNF blockers for (RA) patients should 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.

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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 Rheumatoid arthritis
"Arthritis, Rheumatoid"[Mesh:NoExp] OR ((("Arthritis"[tiab] OR arthros*) AND Rheuma*[tiab]) NOT medline[sb])

#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 "Quality of Life"[Mesh] OR "Quality of Life"[tiab] OR QOL[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])

Limits:
Publication date: 2002/01/01 - present

Search PubMed search 20-09-2010 Result #20
Search #18 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]) Limits: Publication Date from 2002/01/01 918

#19
Search #18 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]) 1048

#18
Search #15 AND #17 1127

#17
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])) 6144918

#15
Search #12 AND #13 AND #14 1511

#14
Search Efficacy[tiab] OR "Treatment Outcome"[Mesh] OR "Drug Toxicity"[Mesh] OR safety[tiab] OR "Costs and Cost Analysis"[Mesh] OR cost[tiab] OR "Quality of Life"[Mesh] OR "Quality of Life"[tiab] OR QOL[tiab] 1211681

#13
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] 76676

#12
Search "Arthritis, Rheumatoid"[Mesh:NoExp] OR ((("Arthritis"[tiab] OR arthros*) AND Rheuma*[tiab]) NOT medline[sb]) 75162

PubMed updated per cochrane review:

Infliximab cochrane review 2002 (gedateerd)

"Arthritis, Rheumatoid"[Mesh:NoExp] OR ((("Arthritis"[tiab] OR arthros*) AND Rheuma*[tiab]) NOT medline[sb])

AND

("infliximab "[Substance Name] OR infliximab[tiab] OR Remicade[tiab])

AND

(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]))

AND

"2002/01/01"[Publication Date] : "3000"[Publication Date])
=> 986 records

Adalimumabcochrane review 2005 => zoekstrategie augustus 2004

"Arthritis, Rheumatoid"[Mesh:NoExp] OR ((("Arthritis"[tiab] OR arthros*) AND Rheuma*[tiab]) NOT medline[sb])

AND

"adalimumab"[Substance Name] OR "adalimumab"[tiab] OR Humira[tiab]

AND

(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]))
=> 404 records

EMBASE.com

#1 Rheumatoid arthritis
'rheumatoid arthritis'/mj

N.B. Als major focus om set te verkleinen.

#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 'quality of life'/exp OR 'quality of life':ti,ab OR QOL: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:
Publication date: 2002/01/01 – present

 # 20-09-2010
'tumor necrosis factor inhibitor'/exp OR 'infliximab'/exp OR 'adalimumab'/exp OR 'etanercept'/exp OR 'golimumab'/exp OR 'certolizumab pegol'/exp AND 'rheumatoid arthritis'/mj AND ('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) AND [2002-2011]/py AND ('drug safety'/exp OR efficacy:ab,ti OR 'drug efficacy'/exp OR 'cost effectiveness analysis'/exp OR cost:ab,ti OR 'quality of life'/exp OR 'quality of life':ab,ti OR qol:ab,ti)

Cinahl

#1 Rheumatoid arthritis
(MM "Arthritis, Rheumatoid")

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

#3 (R)CT en Review filter
Via Limiters

Limits:
Publication date: 2002/01/01 – present

S1 reumatoid arthrithis OR (MM "Arthritis, Rheumatoid")

S2 (MM "Arthritis, Rheumatoid")

S3 (MM "Infliximab") OR (MM "Antibodies, Monoclonal") OR adalimumab OR (MM "Etanercept") OR golimumab OR certolizumab OR remicade OR humira OR simponi

S4 S2 and S3

S5 (MM "Costs and Cost Analysis") OR (MM "Cost Benefit Analysis") OR (MM "Cost Control") OR efficacy OR cost efficiency OR (MM "Safety") OR (MM "Quality of Life")

S6 ((MM "Costs and Cost Analysis") OR (MM "Cost Benefit Analysis") OR (MM "Cost Control") OR efficacy OR cost efficiency OR (MM "Safety") OR (MM "Quality of Life")) and (S4 and S5)

Cochrane

#1 Rheumatoid arthritis
(Arthritis OR arthros*) AND Rheuma*

#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 "Quality of Life" OR QOL OR "drug efficacy"

Limits:
Publication date: 2002/01/01 - present