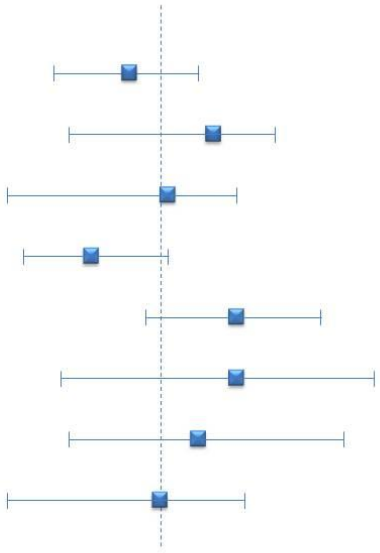
Systematic review and analysis of evidences on clinical efficacy and cost-effectiveness of biological drugs for the treatment of rheumatoid arthritis



Edited by Márta Péntek

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Contents

1 List of tables and figures

2 List of abbreviations

ABA	Abatacept
ACR	American College of Rheumatology
ADA	Adalimumab
AE	Adverse Event
BSC	Best Supportive Care
CI	Confidence Interval
CRP	C-reactive protein
CTZ	Certolizumab pegol
DAS28	Disease Activity Score (28-joint count)
DMARD	Disease Modifying Anti-Rheumatic Drugs
EMA	European Medicines Agency
ETA	Etanercept
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
GOL	Golimumab
HAQ-DI	Health Assessment Questionnaire Disability Index (or HAQ)
INF	Infliximab
LEF	Leflunomide
MCMC	Markov Chain Monte Carlo
MTX	Methotrexate
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR	Odds Ratio
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RR	Relative Risk
RD	Rate Rate
RTX	Rituximab
SD	Standard Deviation
TNF	Tumour Necrosis Factor (alpha)

TOC	Tocilizumab
VAS	Visual Analogue Scale

3 Summary

Technology: Infliximab and comparator biologicals such as abatacept, adalimumab, certolizumab, etanercept, golimumab, rituximab and tocilizumab.

Conditions: Rheumatoid Arthritis (RA).

Issue: Infliximab is registered to be used in patients with RA. The aim of the Report is to evaluate the clinical efficacy and safety of infliximab and comparator biologicals.

Methods: Systematic literature review and analysis as well as meta-analysis of published randomised controlled clinical trials (RCT) were performed, all relevant health economics literature were identified ad analysed.

Results: 338 potentially relevant citations were retrieved and finally after exclusions 40 original RCTs were included in current review. Clinical efficacy of infliximab and comparator biologicals is proved by the available RCTs. Biologics show similar clinical efficacy and safety profile with respect to ACR20, ACR50 and ACR70. Thirty-six cost-utility studies were identified and analysed. Most of the cost-utility analyses were performed in the US (n=8), Northern Europe (n=10) and UK (n=6). These countries differ considerably from Central and Eastern European countries, thus the transferability of these health economic results to jurisdictions of Central and Eastern Europe is rather limited.

Implications for decision making: Scientific evidence suggests that infliximab and comparator biologicals can improve the symptoms of the RA in all important outcomes. Safety profile of these biologicals are rather similar and tolerable. There is a shortage of cost-utility studies published in Central and Eastern European countries, however local data and local study results are more and more required in all CEE countries by the funders. More data about budget impact, costs, outcomes and cost-utility is crucial in order to have better patient access to modern RA therapy.

4 Epidemiology, quality of life and costs in rheumatoid arthritis (Péntek M, Gulácsi L)

4.1 Description of the health problem

Rheumatoid arthritis (RA) is a chronic inflammatory arthropaty associated with articular damage and comorbidities, particularly in the cardiovascular system, and with increasing disability and socioeconomic decline.[74]

RA is thought to result from a combination of genetic susceptibility and exposure to an appropriate environmental trigger.

RA is more common in women than in men and is characterised, pathologically, by an inflammatory reaction and increased cellularity of the lining layer of synovial joints. RA causes pain, swelling and stiffness of affected joints, patients commonly experience joint destruction and fatigue. Productivity loss and work disability is a major problem in RA even today.[107]

The vasculature plays a crucial role in inflammation, angiogenesis, and atherosclerosis associated with the pathogenesis of the disease.[112] As a consequence, patients are at increased risks of myocardial infarction and stroke, both accounts for the observed increased mortality in individuals with RA.[77, 88, 111]

RA patients show a wide spectrum both in terms of disease progression and clinical manifestations.[82] Besides the diversity in natural progression of the disease the burden of RA appears to correlate substantially with socioeconomic and health care system related factors, i.e. GDP and access to treatment in a specific country.[67, 83]

RA related costs are substantial. Healthcare cost is more than €4,000 per patient per year in Western European countries, the cost to patients and families is more than €2,000 yearly.[17] In studies of anti-TNF therapies, the drug costs were higher but the overall costs were lower with these agents. Costs related to lost productivity (indirect costs) highly depend on the methodological approach used however this can be 50% higher than direct costs even if using conservative estimates.[87] Hidden cost (preseenteism, quality of life loss related costs) are often missed in cost-of-illness studies as these are more difficult to measure and evaluate.

4.2 Classification criteria

In the past decades the diagnosis of RA relied on the classification system established by the American College of Rheumatology (ACR) revised criteria from 1987. The criteria were as follows: 1) morning stiffness in and around joints lasting at least 1 hour before maximal improvement; 2) soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician; 3) swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints; 4) symmetric swelling (arthritis); 5) rheumatoid nodules; 6) the presence of rheumatoid factor; and 7) radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints. Criteria 1 through 4 must have been present for at least 6 weeks. Rheumatoid arthritis is defined by the presence of 4 or more criteria[i], and no further qualifications (classic, definite, or probable) or list of exclusions are required.[8]

The importance of early diagnosis and early aggressive treatment of RA became evident in the past years.[91] Therefore, the 1987 ACR criteria have been criticized, because they are not equipped to diagnose early RA. The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) collaboration developed new classification criteria for RA. It aims to arrive at homogeneous groups of patients in order to compare the results of clinical or experimental studies including early RA cases.

In the new criteria set, classification as "definite RA" is based on the confirmed presence of synovitis in at least 1 joint, absence of an alternative diagnosis that better explains the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in 4 domains: number and site of involved joints (score range 0-5), serologic abnormality (score range 0-3), elevated acute-phase response (score range 0-1), and symptom duration (2 levels; range 0-1).[4] Nevertheless, it has been repeatedly shown that the sensitivity of the 2010 criteria increased compared with the 1987 criteria, but the specificity decreased.[118]

[i] These particular criteria are appropriate for established disease, and are not sensitive to early disease.

4.3 Epidemiology

The occurrence of RA varies among countries and areas of the world. The median prevalence estimate for the total population in south European countries is 3.3 (range 3.1 to 5.0) cases per 10^3, for north European countries 5.0 (range 4.4 to 8.0). The median annual incidence for the total population observed in south European countries is 16.5 (range 9 to 24) cases per 10^5. For north European countries the median annual incidence observed was 29 (range 24 to 36).[2] The prevalence of RA among individuals aged 14-65 years was 0.37% in Hungary according to a population based survey.[53] In the Czech Republic (2002-2003) the prevalence of RA was 610/100,000 (95% CI 561 to 658/100,000) and the total annual incidence of RA was 31/100,000 in the adult population aged 16 years and more (95% CI 20 to 42/100,000).[43]

4.4 Health status assessment in RA

Disease activity, functional disability and radiographic damage are the most studied outcomes in RA.

4.4.1 Disease activity

Several validated measures are available to assess disease activity on RA in clinical practice (Clinical Disease Activity Index, Disease Activity Score with 28-joint counts (DAS28), Patient Activity Scale (PAS), PAS-II, Routine Assessment of Patient Index Data with 3 measures, and Simplified Disease Activity Index).[7]

The DAS28 is a combined index which probably the most widely used and has been extensively validated for its use in clinical trials. The DAS28 uses either the erythrocyte sedimentation rate or the C-reactive protein, tender and swollen joint count of 28 joints (arms, hands and knees) and a patient reported global assessment on a visual analogue scale (VAS). (http://www.das-score.nl/)

The DAS28 can be used to assess whether an individual patient has a significant improvement of the disease activity, compared to baseline. It is also possible to choose a baseline

independent absolute level of disease activity as goal for your therapeutic intervention. A DAS28 value of 5.1 (high disease activity) 3.2 (low disease activity) or even 2.6 (remission) are often selected as threshold. The DAS28 plays also crucial role in the assessment of remission.[38]

4.4.2 Functional and health status

4.4.2.1 Health Assessment Questionnaire (HAQ)

The Health Assessment Questionnaire (HAQ) is a valuable, effective, and sensitive tool for measurement of functional status in RA. It is available in more than 60 languages and is supported by a bibliography of more than 500 references.[26] It was developed in 1978 by James F. Fries, MD, and colleagues at Stanford University and it was one of the first self-report functional status (disability) measures. HAQ has become the dominant instrument in RA.

The disability assessment component of the HAQ, the HAQ-DI, assesses a patient's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in eight categories of functioning which represent a comprehensive set of functional activities – dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "Are you able to …" perform a particular task. The patient's responses are made on a scale from zero (no disability) to three (completely disabled). The HAQ-DI score range is between 0-3, the higher score reflects a worse status. HAQ-DI correlates with disease duration and also with disease progression especially in later stages of the disease.

4.4.2.2 EQ-5D

EQ-5D is a standardised instrument for use as a measure of health outcome which was introduced in 1990. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status

(http://www.euroqol.org). The EQ-5D consists of 2 pages - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problem. (A new version has been launched recently with 5 levels.) An EQ-5D health state may be converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. This formula is based on the valuation of EQ-5D health states from general population samples thus EQ-5D index reflects the utility of a health status from the societal point of view. The EQ-5D index ranges between (-0.594) – 1.0, the higher the score, the better the health state is. The EQ-5D is one of the most extensively studied instruments and shows validity and responsiveness for use in RA.[44]

4.4.2.3 HAQ and EQ-5D in economic evaluations

Several studies in various countries confirmed that HAQ correlates not only with disease progression but also with disease related costs in RA.[36, 87] Furthermore, a strong relationship has been proved between HAQ and EQ-5D.[65] Therefore, HAQ has an outlying importance in health economic evaluations. HAQ has been widely used in RA health economic studies to model disease progression, related costs and utilities.[54]

4.4.3 Radiologic measures

Joint damage visualized on radiographs is still the hallmark of RA although there is a growing interest in the use of new imaging techniques (ultrasound, magnetic resonance - MR).[117] Several studies, in pure undifferentiated arthritis and mixed populations, clearly demonstrate that conventional radiographs are helpful in predicting future diagnosis of RA or worse prognosis. However, absence of abnormalities on conventional radiographs does not sufficiently exclude RA or other unfavourable outcome.[60]

Because of the importance of radiographic progression in determining long term outcomes, a standardised, systematic method to evaluate and quantify the amount and progression of radiographic damage caused by RA is desirable. The scoring systems that have been designed to evaluate radiographic changes in RA can be divided into two main groups, global and detailed. The most widely used detailed scoring system is the modified Sharp method and its

variations, and the most widely used global scoring system is the Scott modification of the Larsen score.[84]

4.5 Assessment of treatment response in RA – the ACR response criteria

The ACR developed a core set for of disease activity measures for RA clinical trials. The core set consists of a tender joint count, swollen joint count, patient's assessment of pain, patient's and physician's global assessments of disease activity, patient's assessment of physical function (HAQ), and laboratory evaluation of 1 acute-phase reactant.[37] ACR criteria are indicated as ACR20, ACR50, and ACR70 reflecting 20%, 50%, or 70% relative improvement compared to baseline. Clinical trials report the percentage of study participants who achieve ACR20, ACR50, and ACR70.

More recently, the EULAR/ACR collaboration developed recommendations on how to report disease activity in clinical trials of RA. The recommendation include the following criteria: 1) disease activity response and disease activity states; 2) appropriate descriptive statistics of the baseline, the endpoints and change of the single variables included in the core set; 3) baseline disease activity levels (in general); 4) the percentage of patients achieving a low disease activity state and remission; 5) time to onset of the primary outcome; 6) sustainability of the primary outcome; 7) fatigue.[3]

4.6 Treatment goal in RA

The therapeutic goal in RA should be remission which can be defined in general ‘the state of absence of disease activity in patients with a chronic illness, with the possibility of return of disease activity’ (the treat-to-target concept). Remission is associated with less radiological progression and better functional outcome.[105]

4.7 Drug treatment of RA

Drug treatment of RA comprises three main modalities: disease-modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs). A significant proportion of RA patients can attain a state of very low disease activity

or remission with traditional DMARDs (also called conventional and/or synthetic DMARDs) such as methotrexate (MTX) and leflunomide (LEF), especially if applied in early stage of the disease.

New and highly effective DMARDs have continued to emerge, in particular, biological agents (also called biological DMARDs or Biological Response Modifier Drugs – BRMD) which target tumour necrosis factor, the interleukin 1 (IL-1) receptor, the IL-6 receptor, B lymphocytes and T-cell co-stimulation. Currently eight biological drugs are registered by the European Medicines Agency (EMA) for the treatment of RA: abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, tocilizumab and rituximab (anakinra is registered but available only in few countries, http://www.ema.europa.eu/ema/) Randomized controlled trials (RCTs) have demonstrated the efficacy of biologic agents in treatment of RA. In the past decade various observational cohorts and registries have been created to analyse the effectiveness and safety of biological drugs. Well-designed registries can offer important complementary information to RCTs from real world experience not only in terms of effects and side-effects but also about persistence and costs which are crucial for health economic evaluations.[29]

Treatment strategies have also changed in the past years. Early referral, early institution of DMARD treatment, the treat-to-target concept, tight control using composite measures of disease activity and appropriate switching of drug treatment have been proved to be highly efficacious approaches.[105]

5 Clinical efficacy and safety of biological medications of rheumatoid arthritis (Baji P, Balogh O, Brodszky V)

Summary

Our systematic review – based on fourty randomized controlled trials – showed similar clinical efficacy and safety profile of biologics. All biologics demonstrated statistically significant improvements compared to placebo with respect to ACR20, ACR50 and ACR70 improvements. Among RA patients who took infliximab, etanercept, adalimumab, abatacept, golimumab or rituximab there was no statistically significant difference in 'any adverse events', 'serious adverse events' and 'serious infections' compared to those who received placebo. All three safety endpoints were experienced significantly more frequently with certolizumab compared to placebo and 'any adverse events' was experienced significantly more frequently with tocilizumab.

5.1 Objectives

The main aims of this systematic review were:

1. to identify all relevant literature on clinical efficacy and safety evidence for infliximab and comparator biological medications[i] for rheumatoid arthritis
2. to conduct an up-to-date meta-analysis on clinical efficacy and safety outcomes, and
3. to generate an overview of recently published systematic reviews.

Methods used in this analysis were fully corresponding to NICE Decision Support Unit's recommendations[33] about the evidence synthesis and to Cochrane Handbook's[45] recommendations.

[i] In this report the following terminology are used interchangeably as synonyms: biologic response modifiers, biological, biological medications, biologics, biologic, biologic agent

5.2 Methods

5.2.1 Comparators

The following comparators were considered for this analysis: abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab.

The analysis compares each biological DMARD at licensed dose with placebo both combined with conventional DMARD using follow-up data available at the end of the randomized, double-blind controlled period of the trial. The doses included in the analysis are as follows:

1. Abatacept: 10mg/kg at days 1, 15 and 30 and monthly thereafter, or by patient groups based on patient weight < 60kg, 500 mg; 60 – 100kg, 750 mg; > 100kg, 1000mg.
2. Adalimumab: 40 mg every other week
3. Certolizumab: 400 mg at 0, 2, 4 weeks and then 200 mg at every 2 weeks
4. Etanercept: 25 mg twice weekly, 50 mg once weekly
5. Golimumab: 50 mg once a month
6. Infliximab: 3 mg/kg at 0, 2, 6 weeks and then every 4 or 8 weeks, 6 mg/kg at 0, 2, 6 weeks and then every 8 weeks
7. Rituximab: 1000 mg on days 1 and 15
8. Tocilizumab: 8 mg/kg once every 4 weeks

5.2.2 Search strategies

Electronic databases (Medline and Cochrane Library) as well as references of retrieved articles were searched. The search was not restricted by publication date. The Cochrane Highly Sensitive Search Strategy[45] was applied to identify randomized controlled publications and was combined with ‘arthritis, rheumatoid’ Medical Subject Headings (MeSH) terms and drug names. Meta-analyses were identified by applying the relevant publication type limit. Exact search terms are presented in Appendix 8.1. The search dates were November 1st 2009 to March 31st 2012. References of RCTs from earlier time period were taken from our previous systematic review[19].

5.2.3 Inclusion and exclusion criteria

5.2.3.1 Inclusion criteria

- Randomized controlled clinical trials (RCT) where the full paper can be obtained (studies with only abstracts available were excluded)
- Patients in at least one arm of the trial must receive one of the following treatments: abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab
- Head-to-head trials will also be included.
- The patients of interest are adults with moderate-to-severe RA.

5.2.3.2 Exclusion criteria

- Nonrandomized or uncontrolled studies, observational studies, case series, letters to editor, studies with no abstracts or with conference abstracts only.
- Trials in diseases other than rheumatoid arthritis.
- Studies reporting solely on laboratory measures aimed at investigating disease, or treatment mechanisms and which do not report relevant clinical outcomes.

5.2.4 Data abstraction

Data was extracted and analysed by two independent persons and checked by a third reviewer. Any disagreement was resolved through discussion until consensus was reached. Data on the following outcome measures were included:

Trial characteristics

- Trial/Reference
- Population (description)
- Mean age (years)
- Mean disease duration (years)
- Mean baseline HAQ score (0 to 3)
- Mean baseline DAS28 (scale 0-10)
- Swollen joint count
- Tender joint count
- Trial Duration (weeks)
- Treatment
- Comparator
- Rescue therapy

Clinical Efficacy Measures

- ACR20 (n)
- ACR50 (n)
- ACR70 (n)

Tolerability Measures

- Withdrawals due to adverse events (n)
- Withdrawals for any reason (n)

Safety Measures

- Serious adverse events (n)

- Serious infection (n)
- Any infection (n)

5.2.5 Quality assessment

The quality of selected studies was measured using the Jadad-score.[46] This score is the most frequently used scale in quality assessment of clinical trials.[81] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding, and the withdrawals and dropout of patients. Jadad score ranges from zero to five. Detailed description of scoring can be found in Appendices (Appendix 8.3).

5.2.6 Comparisons

Combining RA trials in a meta-analysis is quite a challenging task. Patient population (previous conventional DMARD history of patients) and administration might differ across trials. There are trials including MTX naïve patients, patients with prior inadequate response to conventional DMARD or patients with prior inadequate response to biologics. Besides, in some trials biologics are used as monotherapy, in other trials they are used in combination with regular DMARD.

Infliximab can be administered only in combination with MTX, therefore only combination therapies were compared in this systematic review.

Two comparisons were done. Firstly, we applied rigorous inclusion criteria and trials comprising patients with prior inadequate response to conventional DMARD were included. Secondly, we applied less rigorous inclusion criteria and trials regardless of patients' DMARD history were included.

5.2.7 Meta-analysis

We have conducted a meta-analysis to compare the efficacy and safety of included biologicals. Two specific analyses were performed for this meta-analysis:

1. direct comparison: a frequentist meta-analysis of study outcomes
2. a mixed treatment comparisons: combining direct and indirect evidence

5.2.7.1 Direct comparison

Data were analysed using Review Manager 5 software. The Relative Risk (RR), Rate difference (RD) and appropriate 95% CI were derived for each study according to the number of events reported in the original studies. Intention-to-treat analysis was conducted. The denominators were the total number of patients randomized; missing values were considered treatment failures. The pooled RR and RD and 95% CI were calculated using a fixed effect model since no significant heterogeneity was detected. The chi-square test for heterogeneity was computed with a P-value set to 0.10 to determine statistical significance. In case of significant heterogeneity random effect model was applied.

5.2.7.2 Mixed treatment comparison

Traditional methods of meta-analysis do not permit indirect comparisons between drugs because they only allow us to pool studies with the same comparators. For our second analysis, we examined the relative effectiveness of each individual treatment using the Lu's method for combining direct and indirect evidence in mixed treatment comparisons, a Bayesian approach. Statistical models developed by NICE Decision Support Unit (DSU) were used. We estimated the posterior densities for all unknown parameters using MCMC (Markov chain Monte Carlo) for each model in WinBUGS version 1.4.3. Each outcome measure was analysed using random effects models, which allowed for studies with 3 or more arms.
All MTC models used the odds ratio as the measure of relative treatment effect and assumed that treatment effects on the odds-ratio scale were multiplicative and exchangeable between trials.

Differences between treatments were considered significant at the 0.05 level if the 95% confidence interval around the odds ratio did not cross 1.

Detailed description of methods and WinBUGS codes are provided in Appendix 8.4.

5.2.7.3 Presentation of results

We give a detailed description of the infliximab trials identified in the literature and also about the quality assessment of each trial. Outcomes of all published infliximab RCT trials will be analysed and combined in one meta-analysis – in this way the key parameters of the "statistical infliximab trial" will be provided. Detailed descriptions of biologics' trials appear in Appendices. Results of the classical meta-analysis will then be summarized. In Appendices, the detailed results from classical meta-analysis will be presented as forest plots diagrams.

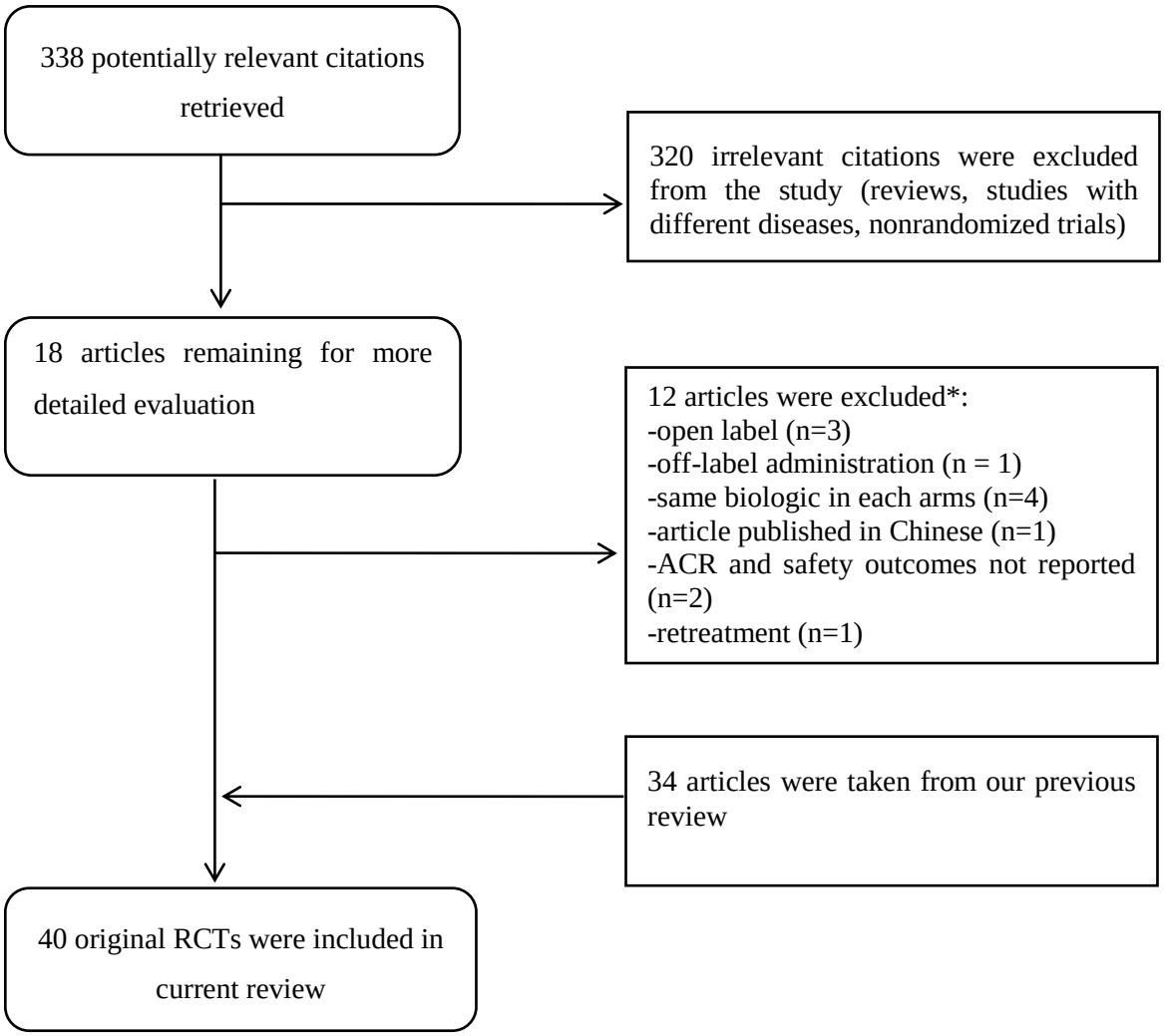
The Bayesian mixed treatment comparison will be introduced separately since it includes indirect comparisons of biologics. Results will be presented by outcome (e.g., ACR20, ACR50, ACR70, serious adverse effect etc.).

5.3 Results: meta-analysis of randomized controlled trials

5.3.1 Included studies

The search in MEDLINE (01.11.2009-31.03.2012) yielded 338 potential citations for randomized controlled trials examining the biological treatment of rheumatoid arthritis. Eighteen RCT reports in rheumatoid arthritis were amongst them from which 12 trials were excluded because they did not meet our inclusion criteria (See Figure 1). In addition, thirty-four references of trials were taken from our previous systematic review.[19] Altogether 40 RCTs were included. The number of trials in given comparisons might be different because of the specific inclusion criteria for each comparison and the distinct endpoints reporting across trials. Detailed descriptions of included studies are provided in Appendices.

Figure 1 Quorum chart for identification of studies in the systematic review



*Detailed explanation for exclusion:

Abatacept: Schiff 2009 ARRIVE[97] – excluded because of open label design; Westhovens 2009[124] - included; Kaine 2012[49] - excluded because of sub cutaneous administration.

Adalimumab: van Vollenhoven 2012[120] - excluded because of open label design; Soubrier 2009 GEUPARD[108] excluded because of open label design.

Etanercept: Kameda 2010[51] – excluded, etanercept in each arm; Kameda 2011[50] – excluded, etanercept in each arm; Golimumab: Kremer 2010[62] - included; Østergaard 2011[85] - excluded, no ACR and safety endpoints.

Infliximab: Takeuchi 2011[114] – excluded, infliximab in each arms; Gao 2010[39] – excluded, Chinese language.

Rituximab: Emery 2010[35] - included; Mease 2010[75] – excluded, rituximab retreatment; Rigby 2011[92] – excluded, ACR and safety outcomes not reported; Rubbert-Roth 2010[93] – excluded, rituximab in each arms; Tak 2011[113] – included.

Tocilizumab: Yacizi 2012[129] - included; Jones 2010[48] – included.

5.3.2 Description of infliximab studies

Four RCTs with infliximab encompassing at total of 2,992 patients were included in this review. The following published papers reported originally these RCTs: Maini 1999 ATTRACT study[68], Clair 2004 ASPIRE study[110], Westhovens 2006 START study[125] and Schiff 2008 ATTEST study[96]. A list of these trials, including comparators, endpoints and baseline patient characteristics are shown in Table 1. Detailed description of infliximab studies are presented in Appendix 8.5. In this section, we will give a short description about study characteristics.

5.3.2.1 Maini 1999 – ATTRACT study

ATTRACT trial[68] was a 30-week, double-blind, multicentre, placebo-controlled RCT that evaluated the effects of infliximab in patients with persistent, active RA despite MTX. Four hundred twenty-eight patients were randomized to receive 3 mg/kg/every 4 weeks or 3 mg/kg/every 8 weeks or 10 mg/kg/every 4 weeks or 10 mg/kg/every 8 weeks infliximab or placebo. All patients received their baseline dose of MTX. Prior to enrolment, patients were required to have ≥ 6 swollen and tender joints, and CRP ≥ 2 mg/dL. Patients were required to have been treated for MTX for at least 3 months with a stable dose of 12.5 mg/week or more, for at least four weeks before screening. The primary endpoint was ACR20 at 30 weeks.

5.3.2.2 Claire 2004 – ASPIRE study

ASPIRE trial[110] was a 54 week randomized, placebo controlled study. The analysis compared the benefits of treatment with MTX and infliximab or treatment with methotrexate alone in patients with rheumatoid arthritis. One thousand forty-nine patients were randomized to receive MTX–placebo or MTX–3 mg/kg infliximab or MTX–6 mg/kg infliximab. Patients were excluded if they had any prior treatment with MTX or other DMARDs within 4 weeks of entry or had been treated with infliximab, etanercept, adalimumab or other anti-TNF agent[i]. Prior to enrolment, patients were required to have 10 swollen and 12 tender joints and CRP

[i] In this report the following terminology are used interchangeably as synonyms: anti-TNFalpha therapy; anti-TNF agent, TNF-blockers; TNF-α blockers

2.0 mg/dL. The primary endpoint was the percentage of ACR improvement (ACR-N) from baseline to week 54.

5.3.2.3 Westhovens 2006 – START study

START study[125] was a 22 week randomized, placebo-controlled trial that assessed the risk of serious infections of infliximab therapy. One thousand eighty-four patients were randomly assigned to receive placebo or 3mg/kg infliximab or 10mg/kg infliximab at weeks 0, 2, 6, 14. All patients had to be received MTX for at least 3 months prior to randomization and had to have active disease in spite of receiving it. The MTX dose must have been stable for at least 4 weeks prior to randomization. Prior to enrolment patients had to have 6 swollen and 6 tender joints. The primary endpoint was the occurrence of serious infections through week 22.

5.3.2.4 Schiff 2008 – ATTEST study

ATTEST trial[96] was a 52 week phase III, randomised, double-blind, double-dummy, placebo- and active (infliximab) controlled multi-centre study that evaluated the efficacy and safety of abatacept or infliximab vs. placebo. Four hundred thirty-one patients were randomised to abatacept 10 mg/kg every 4 weeks or infliximab 3 mg/kg every 8 weeks or placebo every 4 weeks and background MTX. Patients were required to have ≥ 10 swollen and ≥ 12 tender joints and CRP ≥ 1 mg/dL. Patients had to have RA for at least 1 year and had to have an inadequate response to MTX. The primary endpoint was to evaluate a reduction in disease activity, measured by Disease Activity Score 28 with abatacept vs. placebo at 6 months.

Table 1 Characteristics of infliximab RCTs

Author – Study name	Study duration (weeks)	Patients included*	Treatments	Number of patient	Mean age	Disease duration	Baseline HAQ	Endpoints
Maini 1999 - ATTRACT	30	DMARD IR	INF 3 mg/kg/every 8 weeks+MTX INF 3 mg/kg/every 4 weeks+MTX INF10mg/kg/every 8 weeks+MTX INF10 mg/kg/every 4 weeks+MTX placebo + MTX	86 86 87 81 88	56 51 55 52 51	8.4 7.2 9 8.7 8.9	1.8 1.8 1.8 1.5 1.8	**ACR20**, ACR 50, ACR70,
Clair 2004 - ASPIRE	54	MTX naïve	INF 3mg/kg + MTX 0, 2, and 6, and every 8 weeks thereafter through week 46 INF 6mg/kg + MTX 0, 2, and 6, and every 8 weeks thereafter through week 46 placebo + MTX 0, 2, and 6, and every 8 weeks thereafter through week 46	373 378 298	51 50 50	0.8 0.9 0.9	1.5 1.5 1.5	**ACR-N, change in total Sharp score, HAQ**
Westhovens 2006 - START	22	DMARD IR	INF 3 mg/kg+ MTX at weeks 0, 2, 6, and 14 INF 10mg/kg + MTX at weeks 0, 2, 6, and 14 placebo + MTX at weeks 0, 2, 6, and 14	360 361 363	53 52 52	7.8 6.3 8.4	1.5 1.5 1.5	**occurrence of serious infections**, ACR20, ACR50, ACR70, DAS28
Schiff 2008 - ATTEST	52	DMARD IR	ABATACEPT 10mg/kg + MTX INF 3mg/kg every 8 weeks + MTX placebo + MTX	156 165 110	49 49.1 49.4	7.9 7.3 8.4	1.8 1.7 1.8	**DAS28 with abatacept vs. placebo**, DAS28 with inf. vs. placebo; DAS28 with abatacept vs. inf.; EULAR; 6 low disease activity score, HAQ-DI; response rates and mean changes in the physical and mental component summary scores; and eight subscales of the SF-36

DMARD IR: inadequate response to DMARD; MTX=methotrexate

5.3.2.5 Results from infliximab studies

5.3.2.5.1 Efficacy

There was a significant difference at 24 weeks in favour of the infliximab group compared to the placebo group with respect to the ACR20, ACR50 and ACR70 response (See Figure 2, Figure 3 and Figure 4). The NNTs were 5 (3-10), 5 (4-7) and 10 (8-14) treated patients to achieve one ACR20, ACR50 and ACR70 response, respectively.

Figure 2 Efficacy of infliximab 3 mg/kg on ACR20 response at six month

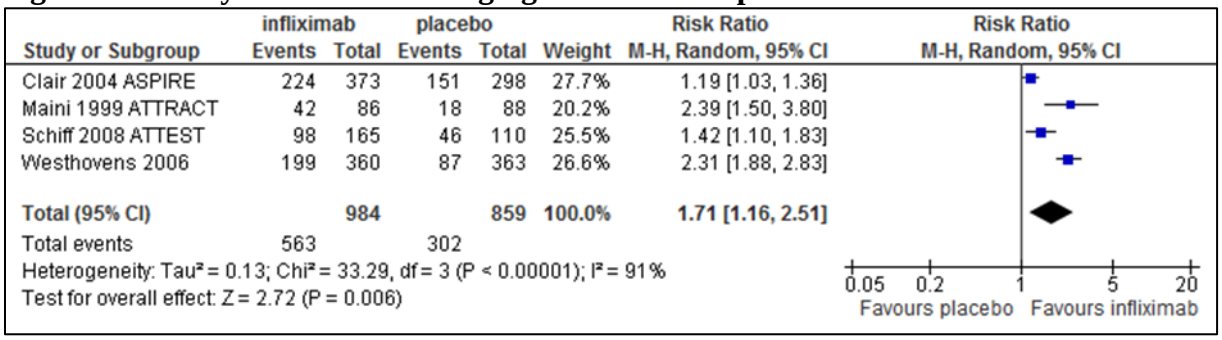


Figure 3 Efficacy of infliximab 3 mg/kg on ACR50 response at six month

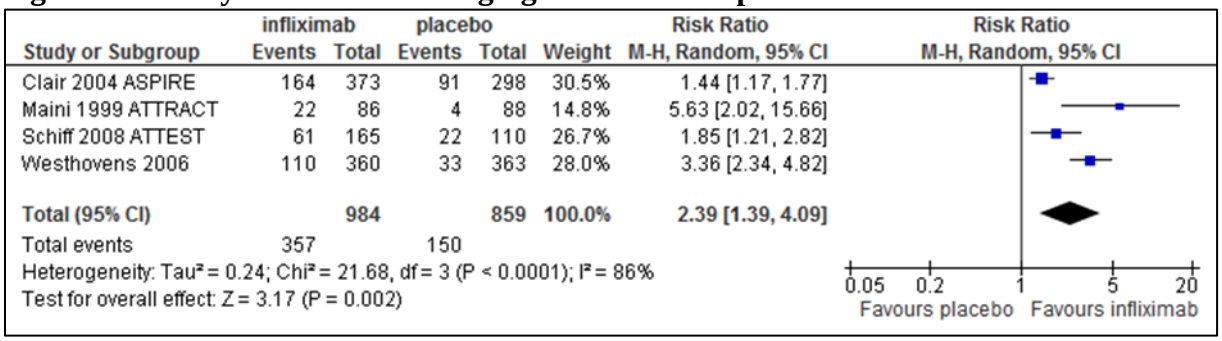
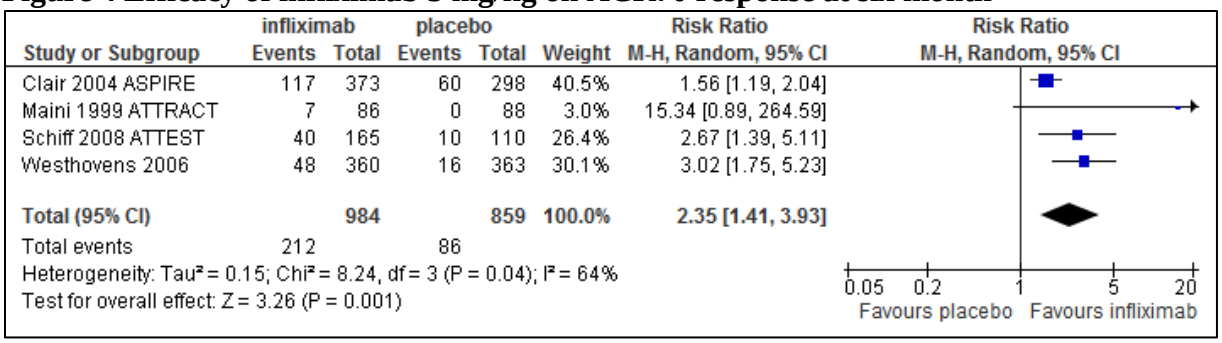


Figure 4 Efficacy of infliximab 3 mg/kg on ACR70 response at six month



5.3.2.5.2 Tolerability and safety of infliximab treatment

There were no significant differences between infliximab and placebo groups with respect to withdrawals due to any reason (Figure 5). There was a significant difference between the two groups with respect to withdrawal due to any adverse events (RR 2.16, 95% CI: 1.18-3.95) in favour of placebo treated patients (Figure 6). There were no significant differences between infliximab and placebo treatment with respect to any AE, serious AE and serious infections (See Figure 7, Figure 8 and Figure 9).

The NNH (number needed to harm) was 25 (17-50) treated patients to cause one withdrawal due to adverse events. Similarly, NNHs were 50 (17-∞), 100 (33--∞) and 100 (33--∞) patients to cause one AE, serious AE and serious infection, respectively. There were no significant differences for safety endpoint of NNH between infliximab and placebo groups.

Figure 5 Tolerability of infliximab 3 mg/kg, withdrawal due to any reason at six month

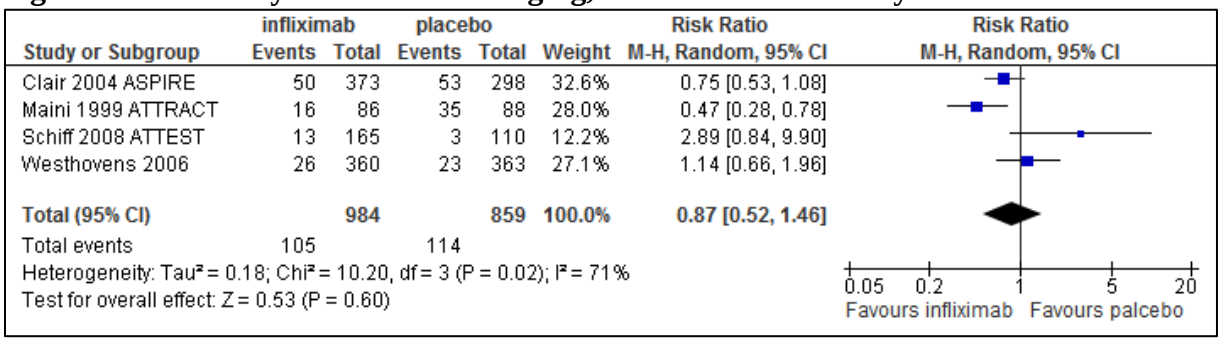


Figure 6 Tolerability of infliximab 3 mg/kg, withdrawal due to adverse events at six month

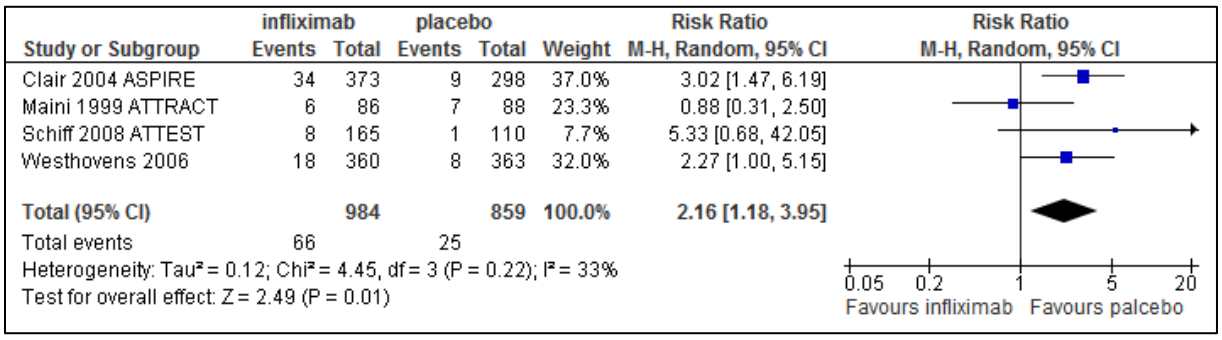


Figure 7 Safety of infliximab 3 mg/kg, any adverse events at six month

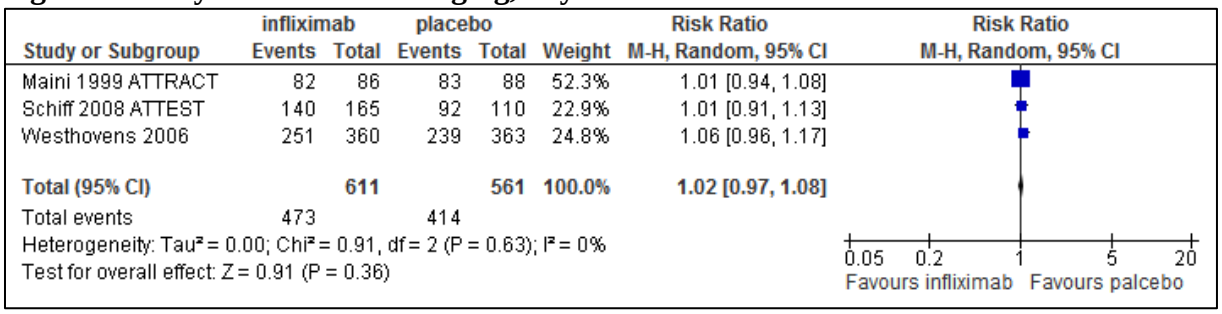


Figure 8 Safety of infliximab 3 mg/kg, serious adverse events at six month

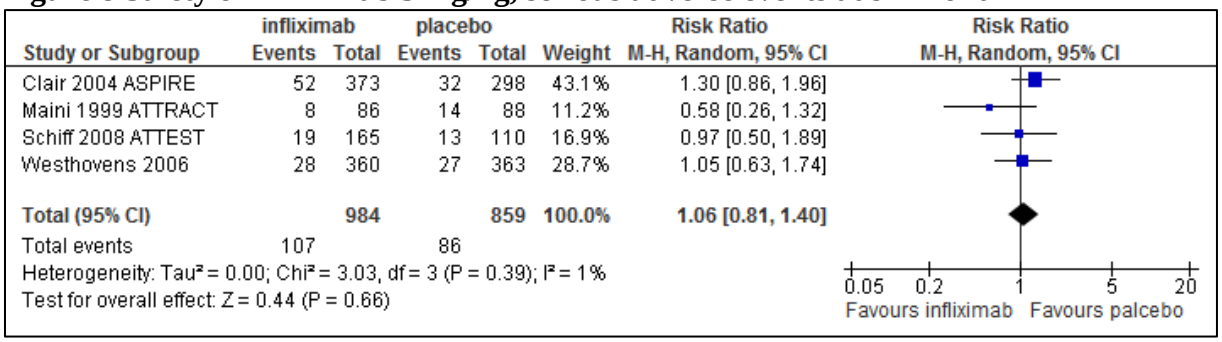
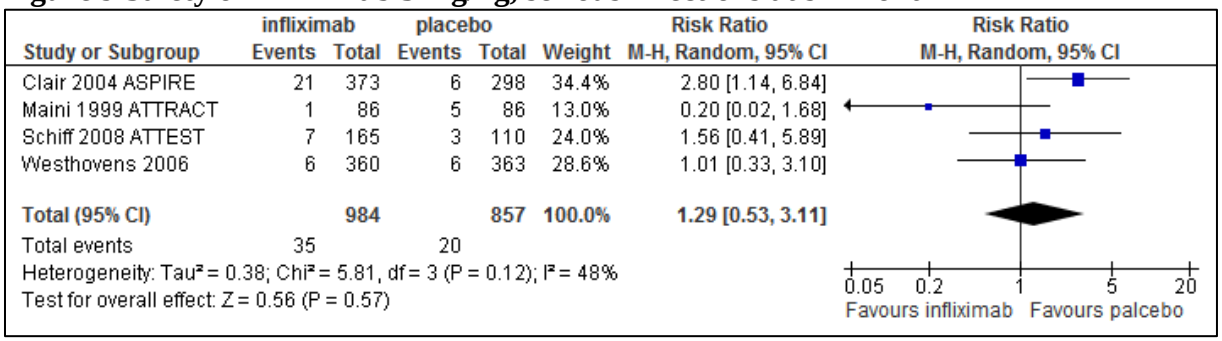


Figure 9 Safety of infliximab 3 mg/kg, serious infections at six month



5.3.3 Classical meta-analysis: efficacy and safety of combination therapy

In total of 31 RCTs were included in current meta-analysis of combination therapy. However, the number of trials in given comparisons might be different because of the special inclusion criteria for a given comparison.

In this section we will present three comparisons with different inclusion criteria and patient population:

1. Biologic + conventional DMARD vs. placebo + conventional DMARD and no restriction on population: In this comparison efficacy endpoints from studies with prior inadequate response to DMARD population, prior inadequate response to biologics population and DMARD naïve population were combined.
2. Biologic + conventional DMARD vs. placebo + conventional DMARD and no restriction on population: In this comparison efficacy endpoints from studies merely with prior inadequate response to DMARD population were combined.
3. Safety and tolerability endpoints: In this comparison safety and tolerability endpoints from studies with prior inadequate response to conventional DMARD population, prior inadequate response to biologics population and DMARD naïve population were combined.

5.3.3.1 Biologic + DMARD vs. placebo + DMARD and no restriction on previous treatment

Thirty-one trials were included in this comparison. Among the 9 excluded trials, only monotherapy was used in 8 trials and efficacy endpoints were not reported in 1 trial.

Each biologic showed significantly more favourable effect than placebo with respect to any ACR response (Table 2).

Table 2 Efficacy of label dose of biologics in combination with conventional DMARD; no restriction on previous treatments

Outcome	Stu-dies	Partici-pants	RR (random effect, 95% CI)	NNT (random effect, 95% CI)
ACR20	**30***	**12716**	**1.93 [1.68, 2.21]**	**4 [3, 5]**
abatacept 10mg/kg	4	1543	1.79 [1.51, 2.11]	4 [3, 4]
adalimumab 40 mg eow.	5	1825	1.82 [1.29, 2.55]	4 [3, 7]
certolizumab 200mg eow.	2	965	5.04 [3.38, 7.52]	2 [2, 2]
etanercept 2x25 mg ew.	3	1090	1.32 [1.06, 1.66]	5 [3, 13]
golimumab 50mg em.	4	1107	1.65 [1.23, 2.21]	6 [4, 10]
infliximab 3 mg/kg e 8w	4	1843	1.71 [1.16, 2.51]	5 [3, 10]
rituximab 2x1000mg	5	1763	1.85 [1.25, 2.73]	4 [3, 7]
tocilizumab 8mg/mg	4	2580	2.45 [1.80, 3.34]	3 [2, 4]
ACR50	**31**	**13225**	**2.67 [2.23, 3.20]**	**5 [4, 5]**
abatacept 10mg/kg	5	2052	2.31 [1.51, 3.54]	5 [4, 6]
adalimumab 40 mg eow.	5	1825	2.94 [1.59, 5.43]	4 [3, 6]
certolizumab 200mg eow.	2	965	6.32 [3.15, 12.66]	3 [3, 4]
etanercept 2x25 mg ew.	3	1090	1.50 [1.19, 1.90]	4 [3, 7]
golimumab 50mg em.	4	1107	2.14 [1.35, 3.38]	8 [5, 13]
infliximab 3 mg/kg e 8w	4	1843	2.39 [1.39, 4.09]	5 [4, 7]
rituximab 2x1000mg	5	1763	2.62 [1.56, 4.39]	5 [4, 7]
tocilizumab 8mg	4	2580	3.97 [2.90, 5.45]	4 [3, 5]
ACR70	**31**	**13225**	**3.27 [2.62, 4.09]**	**8 [7, 8]**
abatacept 10mg/kg	5	2052	2.90 [1.61, 5.23]	8 [7, 11]
adalimumab 40 mg eow	5	1825	3.76 [1.77, 7.99]	6 [5, 8]
certolizumab 200mg eow	2	965	8.24 [3.89, 17.44]	6 [5, 8]
etanercept 2x25 mg ew	3	1090	1.98 [1.50, 2.61]	5 [4, 7]
golimumab 50mg em	4	1107	2.36 [1.39, 4.00]	13 [8, 33]
infliximab 3 mg/kg e 8w	4	1843	2.35 [1.41, 3.93]	10 [8, 14]
rituximab 2x1000mg	5	1763	2.82 [1.61, 4.92]	8 [6, 17]
tocilizumab 8mg	4	2580	8.44 [5.52, 12.91]	6 [5, 8]

*One trial (Westhovens 2009): ACR20 endpoint not reported eow=every other week, ew=every week, em=every month

5.3.3.2 Biologic + DMARD vs. placebo + DMARD and prior inadequate response to conventional DMARD

Twenty-one trials were included in this comparison. Among the 19 excluded trials, only monotherapy was used in 8 trials, efficacy endpoints were not reported in 1 trial, MTX naïve population were enrolled in 6 trials, patients with prior inadequate response to biologics were enrolled in 4 trials.

Each biologic showed significantly more favourable effect than placebo with respect to any ACR response in patients with inadequate response to previous conventional DMARD therapy (Table 3). Biologics were associated with a number needed to treat of 3 to 5 patients for ACR20 improvement. NNTs for ACR50 and ACR70 were between 3-6 and 6-13, respectively.

Table 3 Efficacy of label dose of biologics in combination with conventional DMARD; patient with previous inadequate response to conventional DMARD

Outcome	Studies	Parti-cipants	RR (random effect, 95% CI)	NNT (random effect, 95% CI)
ACR20	**20**	**8168**	**2.07 [1.82, 2.36]**	**3 [3, 4]**
abatacept 10mg/kg	3	1152	1.68 [1.47, 1.90]	4 [3, 5]
adalimumab 40 mg eow.	4	1300	2.05 [1.46, 2.87]	3 [2, 6]
certolizumab 200mg eow.	2	965	5.04 [3.38, 7.52]	2 [2, 2]
etanercept 2x25 mg ew.	1	89	2.67 [1.44, 4.94]	2 [2, 4]
golimumab 50mg em.	2	480	1.82 [1.28, 2.57]	5 [2, 33]
infliximab 3 mg/kg e 8w	3	1172	1.95 [1.36, 2.80]	4 [3, 6]
rituximab 2x1000mg	3	765	1.87 [1.49, 2.34]	4 [3, 10]
tocilizumab 8mg/mg	3	2245	2.11 [1.69, 2.62]	3 [3, 5]
ACR50	**21**	**8677**	**3.05 [2.43, 3.83]**	**4 [4, 5]**
abatacept 10mg/kg	4	1661	2.04 [1.37, 3.03]	5 [4, 6]
adalimumab 40 mg eow.	4	1300	3.49 [2.40, 5.08]	3 [2, 6]
certolizumab 200mg eow.	2	965	6.32 [3.15, 12.66]	3 [3, 4]
etanercept 2x25 mg ew.	1	89	11.69 [1.66, 82.47]	3 [2, 5]
golimumab 50mg em.	2	480	2.43 [1.63, 3.63]	6 [3, 50]
infliximab 3 mg/kg e 8w	3	1172	2.92 [1.69, 5.05]	5 [4, 6]
rituximab 2x1000mg	3	765	2.50 [1.77, 3.54]	6 [4, 13]
tocilizumab 8mg	3	2245	3.67 [2.78, 4.84]	4 [3, 5]
ACR70	**21**	**8677**	**4.19 [2.99, 5.85]**	**8 [6, 9]**
abatacept 10mg/kg	4	1661	2.57 [1.44, 4.59]	7 [6, 10]
adalimumab 40 mg eow	4	1300	4.91 [3.18, 7.58]	7 [5, 10]
certolizumab 200mg eow	2	965	8.24 [3.89, 17.44]	6 [5, 8]
etanercept 2x25 mg ew	1	89	9.82 [0.59, 163.15]	7 [4, 20]
golimumab 50mg em	2	480	3.09 [1.57, 6.09]	11 [5, 0]
infliximab 3 mg/kg e 8w	3	1172	2.97 [1.97, 4.50]	10 [8, 17]
rituximab 2x1000mg	3	765	2.57 [1.50, 4.41]	13 [8, 33]
tocilizumab 8mg	3	2245	8.30 [5.32, 12.95]	6 [5, 7]

ew=every week, eow=every other week, em=every month

5.3.3.3 Safety and tolerability of combination therapy, no restriction on previous treatments

Thirty-two trials were included in this comparison. Eight trials were excluded because biologics were administered merely as monotherapy. The number of trials in given comparisons might be different because of the distinct endpoint reporting across trials.

5.3.3.3.1 Tolerability results

There were significantly less or the same rate of withdrawals due to any reason for biologics compared to placebo (Table 4). There were significantly more withdrawals due to adverse event for infliximab (2.16 [1.18, 3.95]) and certolizumab (2.86 [1.11, 7.33]) compared to placebo. Other biologics showed no significant difference compared to placebo, RRs varied between 0.79 [0.56, 1.10] and 1.61 [1.07, 2.43] (Table 4). Generally, biologics were associated with more withdrawals due to adverse events, with a number needed to treat for harm of 83 [49, 264] patients.

5.3.3.3.2 Safety results

No significant differences in terms of any adverse event were observed between biologics and placebo except of abatacept and tocilizumab, where adverse events were slightly more frequent (Table 5). Serious adverse events were experienced significantly more frequently with certolizumab compared to placebo, our pooled RR was 2.86 [1.11, 7.33]. Other biologics showed no significant differences with respect to serious adverse events compared to placebo. In terms of serious infection, certolizumab and tocilizumab treatment were significantly more unfavourable than placebo, pooled RRs were 4.76 [1.30, 17.46] and 1.81 [1.02, 3.21], respectively.

Table 4 Tolerability of label dose of biologics in combination with conventional DMARD; no restriction on population

Outcome	Stu-dies	Partici pants	RR (random effect, 95% CI)	NNH (random effect, 95% CI)
Withdrawal due to any reason	**29**	**13754**	**0.58 [0.51, 0.67]**	**nv**
abatacept 10mg/kg	6	3493	0.61 [0.44, 0.82]	nv
adalimumab 40 mg/2 weeks	3	1171	0.77 [0.60, 0.98]	nv
certolizumab 200mg	2	965	0.39 [0.30, 0.52]	nv
etanercept 2x25mg/week	3	1090	0.57 [0.41, 0.79]	nv
golimumab 50 mg	3	849	0.54 [0.44, 0.67]	nv
infliximab 3 mg/kg	4	1843	0.87 [0.52, 1.46]	nv
rituximab 2x1000mg	5	1763	0.42 [0.34, 0.51]	nv
tocilizumab 8mg	4	2580	0.66 [0.43, 1.02]	nv
Withdrawal due to adverse event	**30**	**13883**	**1.31 [1.04, 1.64]**	**83 [49, 264]**
abatacept 10mg/kg	6	3493	1.11 [0.74, 1.67]	237 [54, ∞]
adalimumab 40 mg/2 weekst	4	1300	1.41 [0.84, 2.36]	147 [22, ∞]
certolizumab 200mg	2	965	2.86 [1.11, 7.33]	35 [20, 129]
etanercept 2x25mg/week	3	1090	0.79 [0.56, 1.10]	nv
golimumab	3	849	0.92 [0.30, 2.90]	nv
infliximab 3 mg/kg	4	1843	2.16 [1.18, 3.95]	27 [17, 59]
rituximab 2x1000mg	5	1763	1.46 [0.50, 4.29]	114 [34, ∞]
tocilizumab 8mg	4	2580	1.61 [1.07, 2.43]	49 [29, 182]

nv: negative value, lower withdrawal rate in biologic arm

Table 5 Safety of label dose of biologics in combination with conventional DMARD; no restriction on population

Outcome	Stu-dies	Partici-pants	RR (random effect, 95% CI)	NNH (random effect, 95% CI)
Any adverse event	**28**	**13371**	**1.06 [1.02, 1.09]**	**15 [9, 48]**
abatacept 10mg/kg	5	3259	1.04 [1.01, 1.07]	31 [17, 134]
adalimumab 40 mg/2 weeks	4	1695	1.03 [0.87, 1.22]	5 [2, ∞]
certolizumab 200 mg	2	963	1.19 [1.00, 1.43]	9 [4, ∞]
golimumab 50mg	3	849	1.15 [0.88, 1.49]	9 [3, ∞]
etanercept 2x25mg/week	3	1090	0.98 [0.94, 1.03]	nv
infliximab 3 mg/kg	3	1172	1.02 [0.97, 1.08]	47 [16, ∞]
rituximab 2x1000mg	5	1763	1.02 [0.94, 1.11]	57 [11, ∞]
tocilizumab 8mg	4	2580	1.13 [1.05, 1.22]	11 [8, 20]
Serious adverse event	**27**	**13258**	**1.01 [0.88, 1.17]**	**389 [68, -105]**
abatacept 10mg/kg	6	3493	0.90 [0.65, 1.23]	nv
adalimumab 40 mg/2 weeks	2	764	0.85 [0.50, 1.45]	nv
certolizumab 200 mg	2	965	2.14 [1.24, 3.69]	20 [12, 53]
etanercept 2x25mg/week	2	1001	0.84 [0.59, 1.19]	nv
golimumab 50mg	3	849	1.13 [0.56, 2.28]	129 [18, ∞]
infliximab 3 mg/kg	4	1843	1.06 [0.81, 1.40]	183 [29, ∞]
rituximab 2x1000mg	5	1763	0.94 [0.69, 1.29]	437 [33, ∞]
tocilizumab 8mg	4	2580	1.11 [0.71, 1.72]	124 [29, ∞]
Serious infection	**29**	**14171**	**1.31 [1.02, 1.70]**	**121 [71, 425]**
abatacept 10mg/kg	6	3493	1.38 [0.81, 2.33]	167 [69, ∞]
adalimumab 40 mg/2 weeks	4	1679	1.92 [0.59, 6.30]	53 [21, ∞]
certolizumab 200 mg	2	965	4.76 [1.30, 17.46]	32 [20, 70]
etanercept 2x25mg/week	2	1001	0.82 [0.42, 1.62]	nv
golimumab 50mg	3	849	1.07 [0.42, 2.69]	593 [49, ∞]
infliximab 3 mg/kg	4	1841	1.29 [0.53, 3.11]	164 [29, ∞]
rituximab 2x1000mg	5	1763	0.80 [0.44, 1.47]	nv
tocilizumab 8mg	4	2580	1.81 [1.02, 3.21]	60 [36, 179]

nv: negative value, lower adverse event rate in biologic arm

5.3.4 Meta-analysis: mixed treatment comparison

The figures of this section present odds ratios (OR) between treatments A and B in the form treatment A – treatment B. Treatment A is infliximab and treatment B is a biologic agent other than infliximab.

To read the figures:

- for ACR20, ACR50, ACR70, if the point estimate is greater than 1 then the first treatment in the sequence A-B is more effective (although not necessarily statistically significantly more effective)
- for adverse events and tolerability endpoints, if the point estimate is less than 1 then the first treatment in the sequence A-B is safer (although not necessarily statistically significantly safer)

Please note that the confidence intervals provide information on whether the difference between treatments is statistically significant. If the CI contains 1, the difference is not statistically significant.

5.3.4.1 Efficacy

Regarding ACR20 and ACR50 improvements, infliximab showed similar efficacy as other biologics except for certolizumab (See Figure 10 and Figure 11). No significant differences in terms of ACR70 improvements were observed between infliximab and abatacept, adalimumab, etanercept, golimumab or rituximab (See Figure 12). Patients who received certolizumab treatment were significantly more likely to achieve any level of ACR improvements than infliximab. Although, certolizumab studies might be biased because of the extreme high rate of early withdrawal[40], which resulted in a low ACR rate of response to placebo in certolizumab trials and a consequent high ORs. Significantly more patients on tocilizumab treatment met ACR70 endpoint than on infliximab (See Figure 12). It is worthy to point out that three of the seven tocilizumab trials were performed in Asia and these seemed to be reporting more favourable results than trials performed not in Asia as Mandema and his colleagues reported in their meta-analysis.[71]

Figure 10 Indirect comparisons, infliximab vs. biologics in combination with conventional DMARD, ACR20 at six months

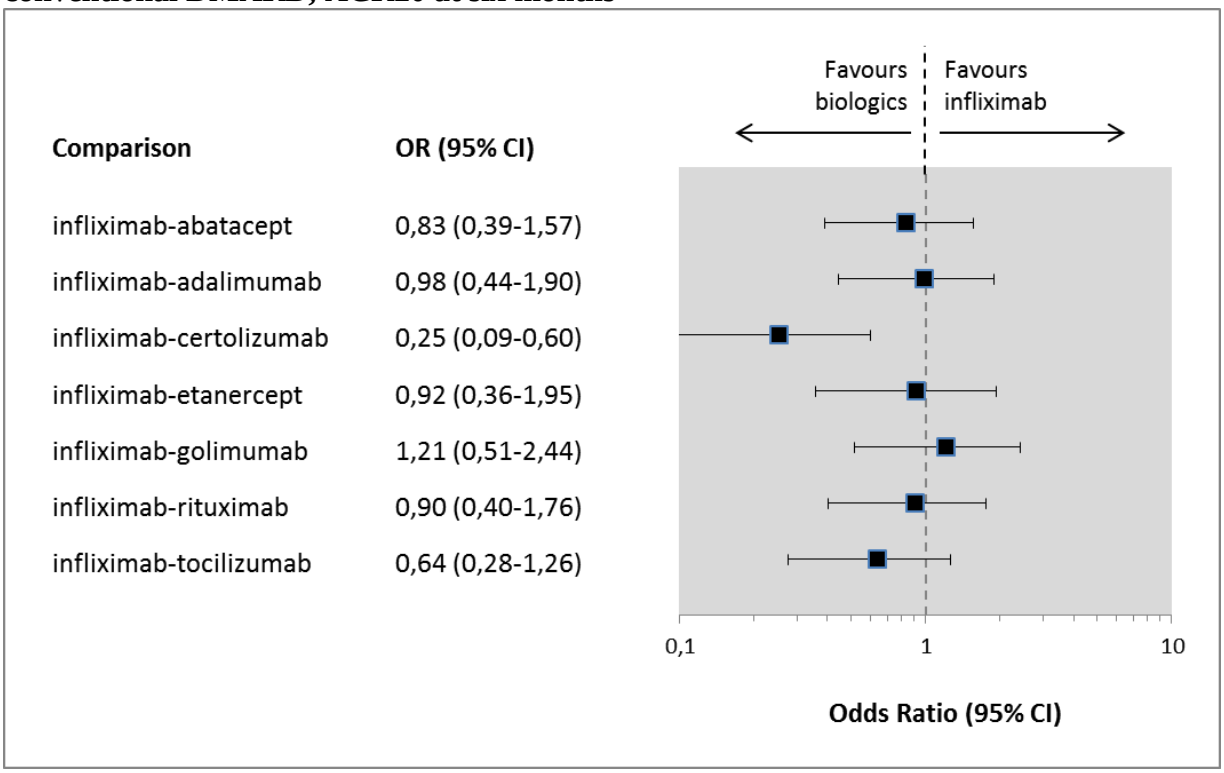


Figure 11 Indirect comparisons, infliximab vs. other biologics in combination with conventional DMARD, ACR50 at six months

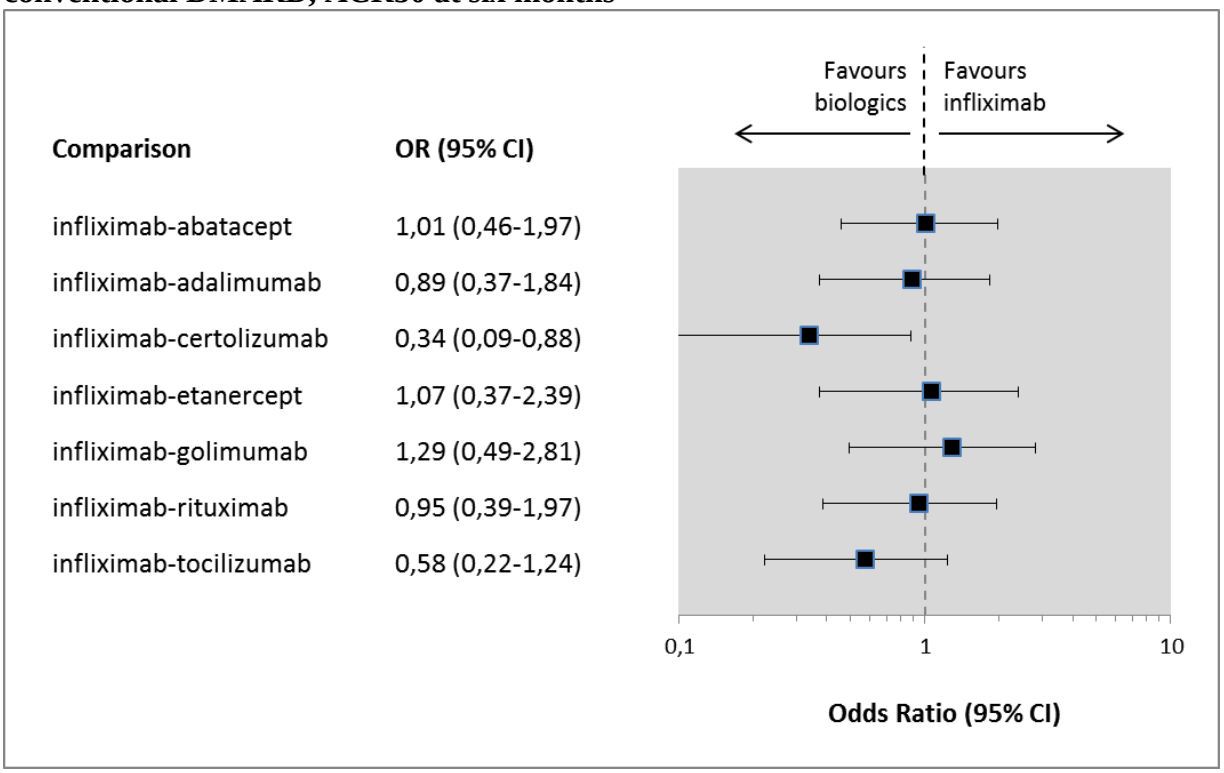
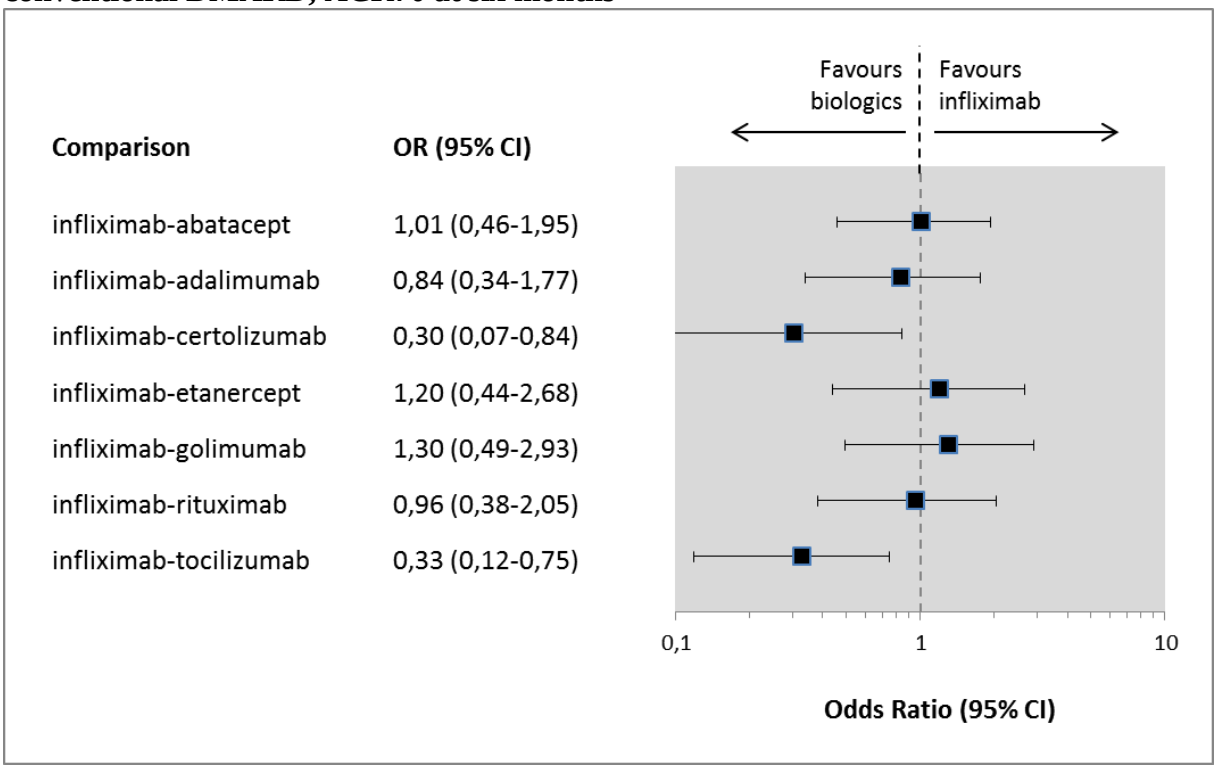


Figure 12 Indirect comparisons, infliximab vs. other biologics in combination with conventional DMARD, ACR70 at six months



5.3.4.2 Safety

No significant differences in terms of serious adverse events and serious infections were observed between infliximab and other biologics (See Figure 13 and Figure 14).

Figure 13 Indirect comparisons, infliximab vs. other biologics in combination with conventional DMARD, serious adverse event at six months

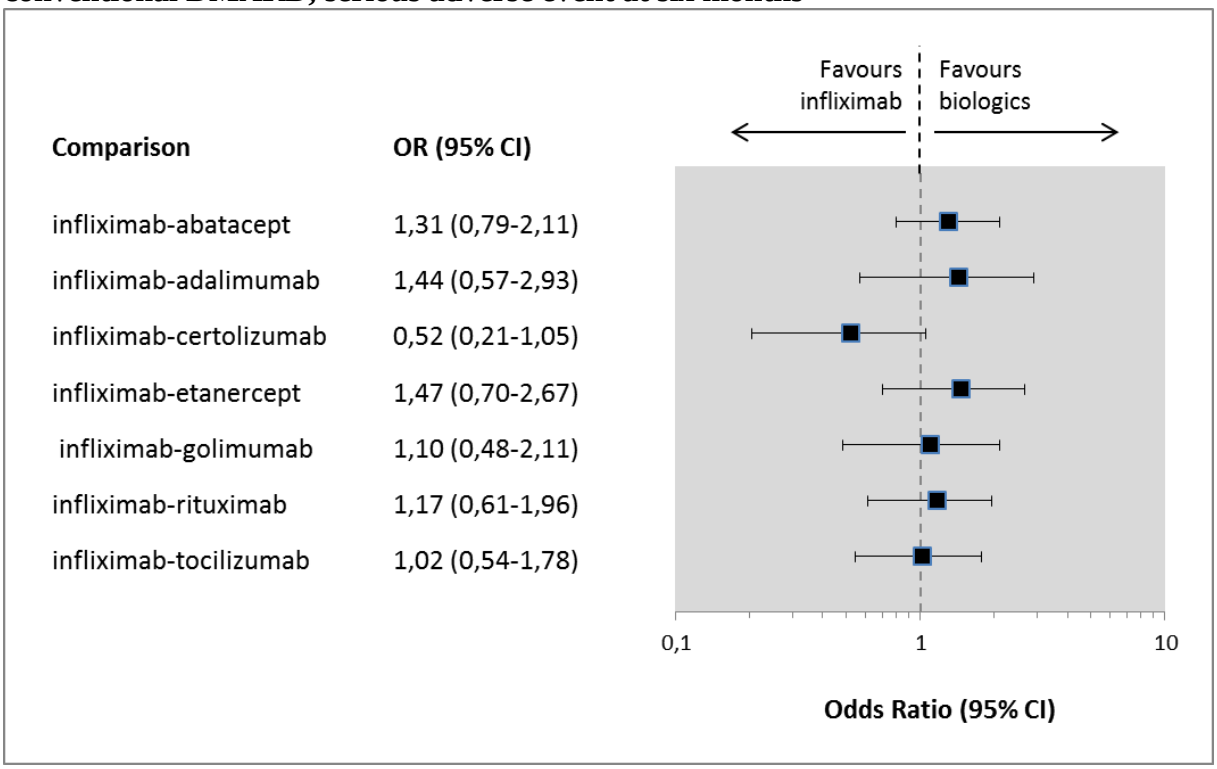
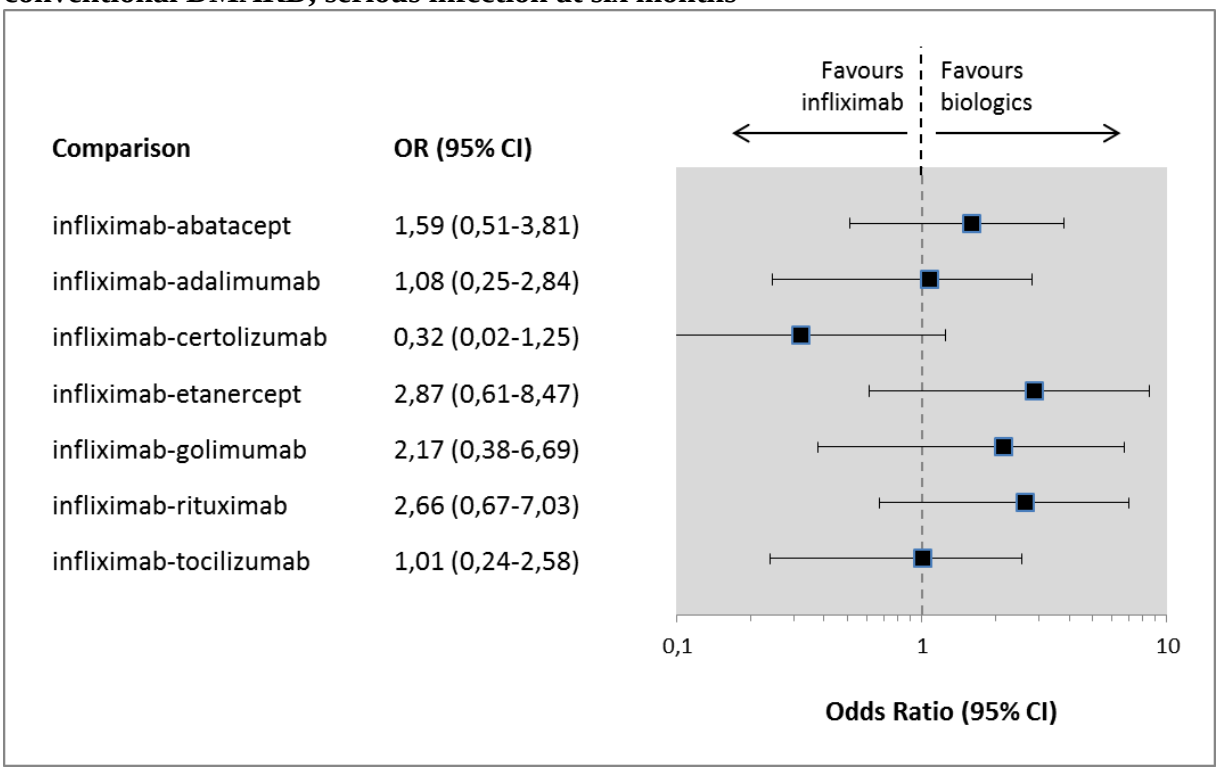


Figure 14 Indirect comparisons, infliximab vs. other biologics in combination with conventional DMARD, serious infection at six months



5.4 Review of previously published meta-analyses

We conducted a MEDLINE search on meta-analysis with biologics in RA published in past five years (2008-2012). All meta-analysis including infliximab were selected for current descriptive review.

5.4.1 Cochrane reviews on biologics

5.4.1.1 Cochrane reviews on efficacy

In the past decade several Cochrane reviews were published which were combining RCTs of a single biological agents[15, 16, 73, 78, 94, 101, 103] In their meta-analysis, Singh and colleagues have been systematically overviewed each previously published and updated Cochrane reviews on biologics.[102] Six biologics - infliximab, etanercept, adalimumab, abatacept, anakinra and rituximab – and 31 RCTs were included in this network meta-analysis. The ACR50 improvement and the number of withdrawals because of adverse events were chosen as main efficacy and safety endpoints by authors.

Regarding efficacy, the number needed to treat (NNT) for ACR50 was 3 for etanercept and infliximab and 4 for abatacept, adalimumab and infliximab. The NNT for anakinra was not significant. Regarding harm, the NNT for withdrawals related to adverse events was 39 for adalimumab, 31 for anakinra and 18 for infliximab. The NNT for abatacept, etanercept and rituximab were not significant.

Authors concluded: "Given the limitations of indirect comparisons, anakinra was less effective than adalimumab and etanercept, and etanercept was safer than adalimumab, anakinra and infliximab."

5.4.1.2 Cochrane review on safety and tolerability – Singh et al. 2011

Main aim of this Cochrane review[104] was to compare the adverse effects of biologics: etanercept, adalimumab, infliximab, golimumab, certolizumab, anakinra, tocilizumab and rituximab in patients with any disease condition except human immunodeficiency disease. One hundred and sixty-three RCTs with 50,010 patients were included. Search was performed until January 2010. The serious adverse event, serious infection, tuberculosis diagnosis,

leukaemia, congestive heart failure, withdrawals due to adverse event or any adverse event were chosen as endpoints for this meta-analysis.

Regarding infliximab, no significant difference compared with placebo in serious adverse events (OR=1.29; 0.98-1.70), serious infection (OR=1.45; 0.99-2.13) and any adverse event (OR=1.33 1.13-1.57) were found. Moreover, biologics were similar to placebo regarding to the occurrence of congestive heart failure and leukaemia, while biologics resulted in significantly more TBC-reactivation.

Authors concluded that "people using biologics in the short term, will probably not experience more serious side effects, serious infections, cancer, or congestive heart failure than people who take placebo".

5.4.2 Comparison of biologics

5.4.2.1 Aaltonen et al. 2012

Five TNF-blockers - infliximab, etanercept, adalimumab, certolizumab and golimumab – and 26 RCTs were included in this meta-analysis.[1] Search was performed until 30.06.2010. Studies with one (or more) of the TNF-blockers delivered the same route and dose as the commercial drug and reported any level of ACR improvement and safety outcomes were included. The ACR 50% improvement and the discontinuation of study due to adverse events at six months were chosen as main efficacy and safety endpoints for this meta-analysis.

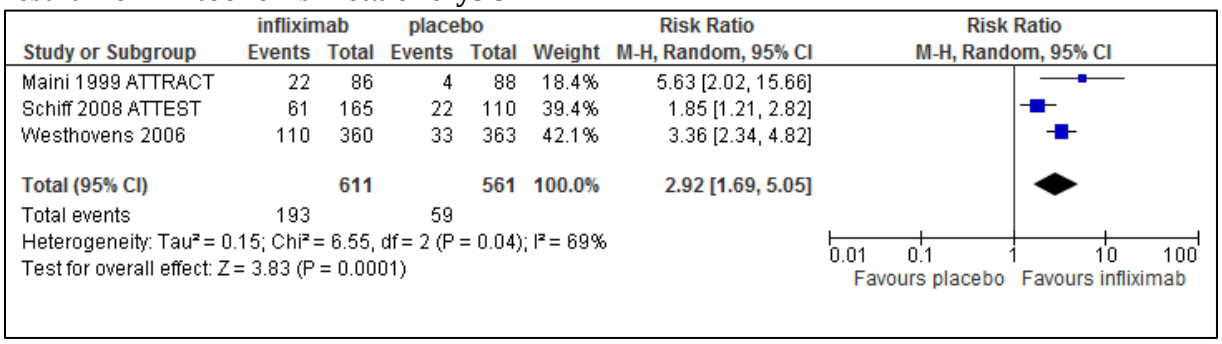
Efficacy

Authors reported non-significant risk ratio for infliximab-placebo comparison at six months (3.08; 95%CI: 0.91–10.43) combining results from two RCTs (Maini 1999 and Schiff 2008). The START study (Westhovens 2006) was excluded from the analysis though it is a randomized, double blind, placebo controlled study reporting ACR50% improvement for 3

mg/kg infliximab at 22 weeks. Authors gave no detailed explanation for exclusion.[i] Combining three studies (Maini 1999, Schiff 2008 and Westhovens 2006), infliximab significantly improves the ratio of patients with ACR 50% response: RR=2.92 (95% CI: 1.69-5.05) (Figure 15).

Authors concluded that "results suggest that infliximab and golimumab do not differ significantly from the control". This conclusion regarding to infliximab is questionable based on our criticism above.

Figure 15 Infliximab vs. placebo at six months, ACR 50% improvement. Recalculating result from Altoonen's meta-analysis



Safety

While the patients on infliximab (3.22, 1.76–5.91), adalimumab (1.59, 1.13–2.23), and certolizumab (2.72, 1.23–6.01), had an increased risk to discontinue, the patients on etanercept (0.71, 0.54–0.92) had a decreased risk. On the other hand, occurrence any adverse events, serious adverse, all infection and any infection were similar at the patients on infliximab and etanercept. Injection or infusion site reactions were more frequent at etanercept.

5.4.2.2 Alonso-Ruiz 2008

Three TNF-α blockers - infliximab, etanercept and adalimumab – and 13 RCTs were included in this meta-analysis.[6] Search was performed until October 2006. Studies with one (or more)

[i] „Patients, interventions, controls, outcomes or design of the studies did not meet the inclusion criteria of the systematic review in 17 publications [30–46]."

of the three TNF-α blockers delivered the same route and dose as recommended in label information were included. Trial duration had to be at least 6 months with efficacy measured by ACR response. ACR20, 50 and 70 improvements were used as efficacy endpoints. The following safety parameters were analysed: any adverse event, withdrawals due to adverse events, serious adverse events, infections, serious infections, infusion or injection-site reactions, malignancies and overall mortality.

Author reported similar effect (ACR20) of TNF-α blockers, combined relative ratios were 1.89 (1.30–2.75) for adalimumab, 1.71 (1.11–2.63) for etanercept and 1.82 (1.19–2.77) for infliximab. ACR50 and 70 improvement at TNF-α blocker treatments were similar, too.

Authors concluded that "patients receiving infliximab showed a higher frequency of serious adverse events (p = 0.048) and infections (p = 0.004)". These results included also off-label dose (10 mg/kg) of infliximab. Later, authors concluded that "the risk of severe infection when receiving high doses of infliximab was significantly increased". According either to our meta-analysis (See Figure 8) or to other published meta-analysis[1, 104, 126, 127], approved doses of infliximab did not cause significantly more frequently serious infection than placebo.

5.4.2.3 Schmitz et al. 2012

Five TNF-α blockers - infliximab, etanercept, adalimumab, golimumab and certolizumab – and 16 RCTs were included in this meta-analysis.[99] Search was performed until October 2010. Studies including MTX naïve patients or patients with early RA were excluded from this analysis. Studies with at least one the TNF-α blocker arm were included, there were no restriction on doses (also off-label doses were included). The ACR20 and 50 and HAQ improvements were chosen as efficacy endpoints for this meta-analysis. A Bayesian mixed treatment comparison model was fitted for each of the outcome measures.

ACR improvements

Combining 16 trials, authors concluded: "All anti-TNF-α agents achieved a significant ACR response over placebo (the credible intervals are higher than, and do not include, 1). The RR for certolizumab achieving ACR20 and ACR50 indicated improved efficacy over

adalimumab, infliximab and golimumab. The outcomes also provide evidence of etanercept being superior to infliximab and golimumab. For ACR50, etanercept appeared approximately equal in efficacy to certolizumab (Cert vs. Eta, RR 1.03); adalimumab shows improvement over infliximab."[99]

HAQ improvements

Combining 13 trials, authors concluded: "all anti-TNF agents show significant improvement over placebo, etanercept achieving the highest improvement (m = 0.31). All anti-TNF agents have greater efficacy than infliximab. Certolizumab and etanercept appear superior to adalimumab. Etanercept shows improved efficacy over golimumab.

These results are in contradiction with findings from earlier meta-analysis. For example, Nixon and his colleagues[79] using the same meta-analysis model, but applying different exclusion and inclusion criteria stated that there were no significant differences between TNF-blockers' efficacy. They reported odds ratios of 0.97 (0.34-2.93) and 0.92 (0.39-2.37) for ACR20 and of 0.98 (0.45-1.93) and 0.96 (0.48-1.9) for ACR50, respectively infliximab-etanercept and adalimumab-infliximab comparisons. These results indicated almost the same efficacy of TNF-α blockers. Also Brodszky used the same model in his previous meta-analysis.[19] He reported no significant differences between TNF-α blockers regarding ACR70 endpoint.

5.4.2.4 Devine et al. 2011

Nine biologic therapies - infliximab, abatacept, anakinra, etanercept, adalimumab, golimumab, tocilizumab, rituximab and certolizumab – and 30 RCTs were included in this meta-analysis.[31] Search was performed until July 2010. Studies in which patients have failed DMARD therapy and had not yet received biologic therapies were included. Studies where patients had previously failed or had an inadequate response to biologics were excluded. ACR 50% improvements at 6 and 12 months was used as efficacy endpoints.

The results of the 6-month analysis showed that the efficacy of each of the nine biologic agents were greater than placebo significantly. According to the indirect comparison,

infliximab was more efficacious than abatacept (OR=1.49), adalimumab (OR=1.20), anakinra (OR=1.79), etanercept (OR=1.15) and golimumab (OR=1.23), differences were not significant. On the other hand, infliximab was less efficacious than certolizumab (OR=0.35), tocilizumab (OR=0.90) and rituximab (OR=0.95), differences were not significant.

5.4.2.5 Wiens et al. 2009

Seven RCTS with infliximab were included in this meta-analysis.[126] Search was performed until March 2009. Studies with infliximab plus methotrexate vs. placebo plus methotrexate comparison were included. The ACR20, 50 and 70 improvement and the discontinuation of study due to adverse events at six months and one year were chosen as main efficacy and safety endpoints for this meta-analysis.

At six months of treatment with infliximab the relative ratios compared to control for ACR20, ACR50 and ACR70 responses were 1.87, 2.68 and 2.68, respectively. Similarly at one year, relative ratios were 2.33, 1.61 and 1.69, respectively. For withdrawals due to adverse events, the relative ratio was 2.05 comparing infliximab and control group.

Author final conclusion was: "This meta-analysis shows a higher efficacy of infliximab relative to placebo without significant safety differences between the infliximab-treated and control groups."

5.4.2.6 Brodszky 2011

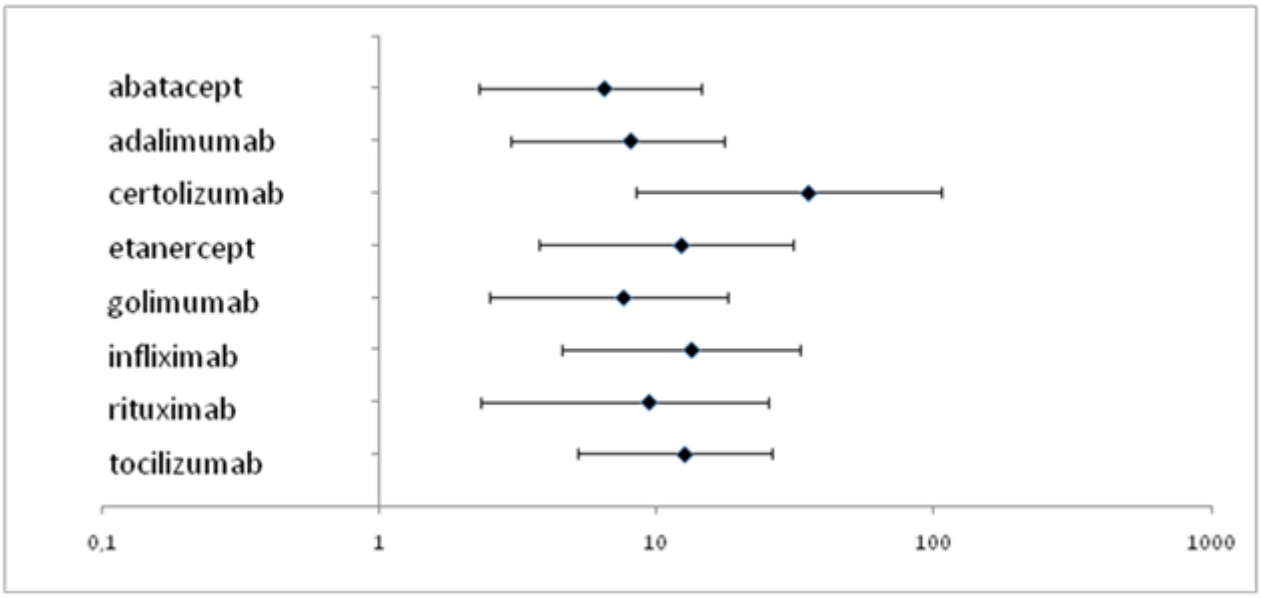
Eight biologics - abatacept, adalimumab, certolizumab, golimumab, etanercept, infliximab, rituximab and tocilizumab – and 32 RCTs involving 18,500 patients were included in this meta-analysis. A Bayesian mixed treatment meta-analysis was conducted. Meta-regression was used to explore the relationship between disease characteristic variables and observed efficacy. The ACR 70% was used by authors as main efficacy endpoints.

According to his results, the relative odds ratios of biological treatments compared to placebo varied between 3.6 to 20.0 and 6.4 to 35.5 in case of biologics monotherapy and combination with conventional DMARD therapy, respectively. Certolizumab was the most efficacious (OR=35.5) followed by infliximab (OR=13.4) (Figure 16). There were no statistically significant differences between biologics except certolizumab-golimumab comparison.

Disease duration and added non-biological therapy were in positive relationship with relative efficacy. More severe disease resulted smaller relative effect.

The author's main conclusion was the following: "The results show that efficacy of biological treatments are similar. The relative efficacy worsens with more severe disease and improves with disease duration."

Figure 16 Relative efficacy of biologics combined with conventional DMARD; ACR70 response. Effect of different disease duration and baseline HAQ score across studies were eliminated.



Source: Brodszky 2011

5.4.2.7 Launois et al. 2011

Seven biologics - infliximab, etanercept, adalimumab, golimumab, certolizumab, anakinra and tocilizumab – and 19 RCTs were included in this meta-analysis.[63] Main objective was to compare certolizumab with other biologics. Search was performed until 30th of June 2009. RCTs including patients with RA who had an inadequate response to DMARD were enrolled by authors. In addition, the studies evaluated labelled doses of biologics versus placebo in combination with continuation of inadequate conventional DMARD. The ACR 20%, 50% and 70% improvement at 24±8 weeks were chosen as efficacy endpoints for this meta-analysis. Indirect comparison was carried out using a multiple-treatment Bayesian mixed treatment comparison model.

Each biologics were significantly more efficacious than placebo regarding of any ACR endpoints. For ACR20, 50 and 70 responses, ORs for infliximab were 3.31 (2.05–5.03), 3.59 (1.97–6.13) and 3.55 (1.77–7.15), respectively. Certolizumab and etanercept had the highest ORs. While, number of patients in etanercept studies was the lowest in this meta-analysis, for example etanercept studies included 240 patients and infliximab studies included 1,345 patients. Regarding to certolizumab, authors did mention in limitations but certolizumab studies might be biased because of the extreme high rate of early withdrawal.[40] Author mentioned the low ACR20 rate of response to placebo in certolizumab trials as a limitation. Low placebo response rate was the consequence of early withdrawal and resulted in high ORs.

Authors' main conclusion was following: "Results of this original multiple-treatment Bayesian meta-analysis indicate that certolizumab pegol is at least as efficacious as the preexisting antirheumatic anticytokine biotherapies."

5.4.3 Switching

5.4.3.1 Remy et al. 2011

Treatment effect of switching from one TNF-α blocker to another TNF-α blocker was analysed in this study.[90] It was not a "regular" meta-analysis combining RCTs, but a meta-analysis combining mainly uncontrolled and open label prospective cohort studies. Direct results from RCTs on switching are rare therefore we found useful to mention this analysis. Thirty-two studies with three TNF-α blocker – adalimumab, etanercept and infliximab – involving 4,441 patients were included by Remy and his colleagues. The ACR 20%, 50% and 70% and EULAR improvement were chosen as efficacy endpoints.

The amount of available information on switching was unevenly distributed between potential switches. Much more data were available on switching from infliximab to adalimumab or etanercept (22 studies with 2,152 patients) than on reverse directions (7 studies with 82 patients). The pooled percentage of responders according to ACR 20%, 50% and 70% and EULAR response were 55.1%, 31.5%, 13.8% and 74.9%, respectively. Author concluded: "This meta-analysis suggests that switching to a second TNF-α inhibitor is clinically relevant in RA. Response to a second TNF-α inhibitor appears to be slightly better if the first TNF-alpha inhibitor was discontinued because of adverse events."[90]

5.4.3.2 Alivernini et al. 2009

Efficacy of switching from any biologics to any other biologics was examined in this meta-analysis.[5] Search was performed until December 2008. Clinical trials in RA were included in the analysis if a second biologic was used in the trial after failure of a first biologic. The ACR 20%, 50% and 70% improvement and DAS remission were chosen as efficacy endpoints for this meta-analysis.

Results on switching to infliximab showed that after inadequate response to etanercept, 62% and 31% of patients receiving infliximab achieved ACR20 or ACR50 response. On the other hand, 29% and 14% of patients remaining on etanercept treatment achieved ACR response.

Authors concluded regarding of major outcome (ACR70 and DAS remission): "The efficacy of a second biological agent, irrespective of the mode of action, in reaching an ACR70 or DAS remission after a first biologic is observed from 5% to 15% and from 9% to 15.4%, respectively." Authors emphasized that few studies had strong evidence, most of the studies were open-label and included small number of patients.

5.4.3.3 Malotti et al. 2011

Five biologics - infliximab, etanercept, adalimumab, abatacept and rituximab – and 35 clinical studies (RCTs, open label or uncontrolled studies) were included in this meta-analysis.[70] Search was performed until July 2010. Both randomized and non-randomized studies were included. Efficacy of switching to TNF-α blockers from other biologics was assessed based on nine non-randomized studies. TNF-α blocker switches were efficacious. The quality of evidences was poor.

5.4.4 Dose escalation

5.4.4.1 Mandema et al. 2011

Main aim of this review[71] was to analyse the dose-dependent efficacy of biologics. Nine biologics - abatacept, adalimumab, anakinra, certolizumab, golimumab, etanercept,

infliximab, rituximab and tocilizumab – and 50 RCTs involving more than 21,500 patients were included in this meta-analysis. A regression method based on dose–response relationships to account for differences in efficacy as a function of dose was used by authors.

Efficacy of each biologics was in a positive relationship with doses. Higher doses resulted in higher rate of ACR response. Authors concluded: "The analysis showed that all anti-TNFs share the same dose–response relationship for ACR 20, 50, and 70, differing only in their potency."

5.4.5 Age and treatment effect

5.4.5.1 Köller et al. 2009

Treatment effect with TNF-blockers in different age was analysed in this study[61] by Köller and his colleagues. Patient-level data from two large RCTs of adalimumab and infliximab (ASPIRE and PREMIER trials) were analysed. Age quartiles of pooled study populations were compared the following age groups were compared: 18–41, 42–50, 51–60 and 61–82 years. Calculated composite indexes, HAQ score and radiological scores were compared between age groups at baseline and one year.
Authors did not find a correlation between age and treatment response. They concluded that the efficacy of biologics in elderly RA patients is comparable with that in younger patients. They suggest that physicians should not use patients' age to limit their therapeutic options.

5.5 Conclusions

5.5.1 Efficacy and safety

Our review delivers results from both direct and indirect comparisons of the clinical efficacy and safety of 7 biologics for rheumatoid arthritis based on published double-blind, placebo-controlled trials. Firstly, a number of classical direct meta-analysis were undertaken to obtain summary estimates of clinical effectiveness and safety parameters. Following the recent NICE

guidelines, mixed treatment comparisons were conducted allowing for indirect comparisons in the absence of head-to-head trials.

The systematic search identified forty RCTs. Most studies were of good internal validity and compared one biologic to placebo (with or without methotrexate).

Generally, biologics showed similar clinical efficacy and safety profile. The meta-analysis showed that all biologics demonstrated statistically significant improvements compared to placebo with respect to ACR20, ACR50 and ACR70 improvements. No statistically significant differences could be seen between most of the biologics including infliximab and placebo with respect to any adverse events, serious adverse events and serious infections. All three safety endpoints were experienced significantly more frequently with certolizumab compared to placebo and any adverse events were experienced significantly more frequently with tocilizumab.

Our mixed treatment analysis indicated that infliximab was associated with a lover ACR70 response rate compared to certolizumab and tocilizumab and with a lover ACR20 and ACR50 response rate compared to certolizumab. At the same time, certolizumab was associated the highest rate of serious infection and adverse events. Although, certolizumab studies might be biased because of the extreme high rate of early withdrawal[40], which resulted in a low ACR response rate and adverse events rate to placebo in certolizumab trials and a consequent high ORs.

5.5.2 Limitations

A potential weakness of this meta-analysis arises from the fact that the trials from which data are combined are likely to differ in their design and patient population characteristics.

6 Biological therapies for the treatment of RA – systematic review of the health economic literature (V. Hevér N)

Summary

Our systematic review revealed thirty-six cost-utility analyses of biological therapies for RA. The majority of the studies (n=19) evaluated biological treatment for RA patients who have already failed at least one traditional DMARD therapy, eight considered those who have failed at least one biological drug. However the number of studies involving DMARD naive RA patients was rather substantial as well (n=9). There was extensive methodological heterogeneity across the selected health economics evaluations. The key issue is the transferability of the results from these health economics studies to very different jurisdictions of Central and Eastern Europe.

6.1 Literature search

We performed a literature search for health economic evaluations of abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab for the treatment of RA. The search included the time period between 2008 and April 2012 and ran in the following databases: Ovid MEDLINE(R) 1946 to Present with Daily Update, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Web of Knowledge and Centre for Reviews and Dissemination (CRD). The search strategies applied are presented in Appendix 8.7.

Original articles of full economic evaluations presenting cost-utility data (cost/QALY) of biological therapies (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) for RA were retrieved by two independent reviewers.

Articles with full text in English or German were analysed. Data were extracted using a standard collection form and are presented in a table format but also short descriptive summary of each is provided. Quality of the economic evaluations was assessed using the checklist developed by Drummond et al.[34]

Articles written in other language than English or German (but fulfilling our inclusion criteria based on their title and English abstract) are listed as potentially relevant publications.

Cost-utility analyses form before 2008 were captured by a review article.[119] Van der Velde et al. performed a systematic literature search for cost-effectiveness studies of biological drugs (etanercept, infliximab, adalimumab, anakinra, abatacept, rituximab, natalizumab, golimumab, and efalizumab) compared to any DMARD for RA.[119] The electronic literature search was closed in the 3rd quarter of 2008. Altogether 18 health economic evaluations were selected, 16 of them were cost-utility analyses which were included in our current report.

6.2 Results

Our search resulted 450 hits, 23 articles fulfilled our inclusion criteria.

The number of hits and included articles were as follows (articles overlapping between databases are listed only where first appeared):

- Ovid MEDLINE(R) 1946 to Present with Daily Update – 85 hits / 17 articles included[12, 14, 23, 30, 42, 52, 57, 64, 66, 76, 89, 95, 100, 116, 121, 122]

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations – 15 hits / 2 articles included[32, 106]

- Web of Knowledge – 250 hits / 3 articles included[13, 58, 70]

- Centre for Reviews and Dissemination (CRD) -100 / 1 included article[98].

The list of hits and reasons of exclusion are presented in Appendix 8.8.

Among the 23 articles 1 was in Czech and 1 in Russian and the full text was not available for 1, thus we performed detailed analysis of 20 publications and provide only abstract for the other three.

The systematic review by Velde et al. included 16 articles analysing the cost-utility of adalimumab, etanercept or infliximab, no studies on rituximab or abatacept were identified. [119]

In the next sections first we give a summary of the 16 cost-utility studies (time period: - 2008) discussed by Velde et al.[119] Then a short description of the 20 articles from our additional search (2008-2012) is provided. Main data (characteristics and results) of the analysis are presented also in tables using a standardized extraction format. (Table 6, Table 7, Table 8) Quality assessment of the economic evaluations according to the Drummond checklist is presented separately. (Table 9, Table 10, Table 11)

6.2.1 Systematic review by Velde el al. (2011)

In this systematic review[119] incremental cost-effectiveness ratios (ICERs) were stratified by biologic agent and indications for the use of biologics in RA patients.

Sixteen cost-utility studies were involved[9-11, 18, 27, 28, 47, 55, 56, 59, 72, 109, 115, 123, 128]:

- DMARD naive patients: five studies evaluated a DMARD sequence containing a biologic agent compared to a DMARD sequence without biologics in patients with no previous DMARD experience (one study focused on early RA patients)
- Patients with MTX failure: three studies evaluated biologic combination therapy in methotrexate-resistant patients
- Patients with min. 2 DMARD failures: eight evaluations analysed the cost-utility of inserting a biologic monotherapy or combination therapy into a DMARD sequence compared to a DMARD sequence in patients who failed at least 2 DMARDs.

Biologic agents evaluated included adalimumab, etanercept, and infliximab, either as monotherapies or combination therapies and one study evaluated biologics as a class (tumour necrosis factor-alpha antagonists). Authors did not identify evaluations of the interleukin-1

receptor antagonist anakinra, second-generation biologics (e.g., abatacept, rituximab) or the lately registered agents (golimumab or certolizumab pegol).

Biologics were compared to DMARD monotherapies, combination therapies, DMARD sequences and mixed drug treatments that included DMARDs and other drugs. There was extensive heterogeneity across the selected evaluations in terms of characteristics of the patient population and methods applied. Most evaluations were conducted in the US (n=5), UK (n=4), Sweden (n=3), Canada (n=2), The Netherlands (n=1) and Japan (n=1). Economic perspectives included societal (n=8) and payer (n=11). Most evaluations considered a lifetime time horizon (n=10). All of the studies considered direct costs, 9 incorporated indirect costs as well. All cost-utility studies used model-based analytic approaches. Efficacy data from the Anti-Tumour Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) were used in all of the studies that evaluated infliximab, except 3 studies that used registry or other data. Similarly RCT data for etanercept and adalimumab were the most frequently applied.

The quality of life weight most often used to calculate QALYs was a score derived from the EQ-5D Index (and one missed to identify the utility used), weights were mainly (n=10) derived by transforming HAQ scores using linear regression.

ICERs were converted and presented in 2009 Canadian dollars by the authors.

In patients with no previous DMARD experience (biologic DMARD sequence vs. traditional DMARD sequence) no studies were conducted from the societal perspective. The median ICER from the payer's perspective varied between $270,000 and $77,000 per QALY depending on the position of the biologic drug within the sequence (the later the more beneficial), and the overall median ICER was $130,000/QALY. (The median ICER of infliximab + MTX was $142,000/QALY [range $100,000 –$169,000/QALY].)

In patients who failed methotrexate monotherapy (biologic combination therapy versus methotrexate monotherapy) 3 studies evaluated biologic combination therapy (infliximab+MTX), all the three took the societal perspective and 2 studies also took a payer

perspective.[56, 72, 128] Efficacy data were retrieved from the ATTRACT trial. ICER values ranged from $6,000–$92,000/QALY.

In patients who failed at least 2 DMARDs eight evaluations estimated the cost-utility of inserting a biologic monotherapy or combination therapy into a DMARD sequence compared to a DMARD sequence. All of them took the societal perspective (one performed the analysis from the payer perspective as well). ICER values varied highly within a range of $45,000–$612,000/QALY. Median ICERs by biologic drug were $81,000/QALY for adalimumab, $79,000/ QALY for adalimumab+MTX, $127,000/QALY for etanercept, $75,000/QALY for etanercept+MTX, and $133,000/QALY for infliximab+MTX. There were no consistent trends across the results.

Authors conclude that at a willingness to pay threshold of $50,000 per QALY gain (Canada 2009), biologics were not cost effective in patients with no previous DMARD exposure and patients who failed MTX combination therapy or sequential DMARD administration. Evidences suggest cost-effectiveness in patients who failed MTX monotherapy, nevertheless, this might be partly due to the choice of comparator, where methotrexate-resistant patients continued to receive methotrexate.

6.2.2 Analysis of the articles revealed by the additional search

The 20 articles were stratified by patient groups:

- DMARD naive patients: 4 articles[30, 57, 98, 116]
- RA patients with synthetic DMARD failure: 8 articles[32, 58, 64, 95, 100, 106, 121, 122]
- RA patients with biologic DMARD failure: 8 articles[14, 23, 42, 52, 66, 70, 76, 121]

6.2.2.1 Methotrexate naive RA patients

Davies et al., United States (2009) – TNF-α antagonists[30]

The objective of this study was to estimate the comparative lifetime cost-effectiveness of sequenced therapy with TNF-α antagonists as the initial therapeutic intervention for patients with early RA.[30] The model following a structure described by Bansback et al.[9] examined costs and clinical outcomes over a course of five competing sequential regimens, rather than by comparing single agents against another:

- a reference sequence without biologic therapy
- 3 sequences with a single biologic followed by traditional DMARD
- a dual biologic sequence in which treatment was initiated with adalimumab+MTX followed by etanercept monotherapy (within a supplementary analysis)

In the base case analysis the adalimumab-plus-MTX-initiated sequence resulted in the greatest number of QALY (3.24). When the adalimumab-plus-MTX-initiated sequence was followed by etanercept before switching to other DMARD, the number of QALY was increased by one-third over the course of therapy (4.22 QALY vs 3.24 QALY). Regarding the ICERs, the sequences of etanercept and infliximab+MTX were extendedly dominated by the adalimumab-plus-MTX-initiated sequence. Comparing DMARD and single TNF-sequences, the adalimumab-plus-MTX-sequence provided the greatest ICER of US $47,157 per QALY. When productivity costs included, the infliximab-plus-MTX-sequence was dominated by the etanercept sequence, although both remain extendedly dominated by the adalimumab-plus-MTX-sequence for which ICER was US $23,377 per QALY compared with the etanercept sequence.

According to the supplementary analysis, the strategy of treating with etanercept as a second-line TNF-antagonist subsequent to first-line adalimumab could yield an additional QALY compared with adalimumab and extendedly dominated all single TNF-strategies, at a cost of US $42,727 per QALY and US $19,663 per QALY if productivity was included. At US $50,000 considered a minimum cost-effectiveness threshold in the US adalimumab-plus-MTX therapy was found to have a 70% probability of being cost-effective.

The results of sensitivity analyses demonstrated how the cost-effectiveness of adalimumab versus DMARD changed with varying assumptions:

- applying a EQ-5D utility regression by Kobelt, et al increased the cost per QALY of adalimumab to US $65,000
- when the HAQ progression was assumed to be twice or when the withdrawal rate from DMARD therapy was half both that applied in the base case, cost per QALY was also between US $60,000 and US $70,000
- radiographic progression evidence suggests that TNF-antagonists may arrest disease progression to the extent that the HAQ score remains stable during periods of continued response. This scenario produced the lower ICER for adalimumab of US $36,000.
- other sensitivity analyses produced cost per QALY for adalimumab versus etanercept of between US $42,000 and US $54,000.

The analysis outlined above had 3 primary limitations:

- ERA trial data were used to model responses to etanercept monotherapy as combination therapy with MTX was not studied in the ERA
- the model did not consider the influence of delays in treatment initiation for early ERA
- the study suffered from a paucity of evidence on the effectiveness of traditional DMARD

This model based analysis showed that of the 3 TNF-antagonists, adalimumab had the most favourable cost-effectiveness, whether used as initial therapy followed by DMARD or followed sequentially by another TNF-antagonist.

Van den Hout et al., The Netherlands (2009) - infliximab[116]

The objective of this study was to evaluate societal costs and QALYs of four treatment strategies for patients recent-onset active RA (sequential monotherapy, step-up combination therapy, initial combination therapy with prednisone, or initial combination therapy with infliximab – BeST trial).[116] The study differs from previous ones at certain points:

- the article based on the observational data of BeSt study while previous ones were all modelling studies, combining different types of data from different sources
- previous studies all compared fixed medication therapies, whereas the study of Van den Hout et al. compared dynamic strategies, intensifying or tapering medication based on the patient's status
- the study contained exclusively cost-utility analysis

As for the results, in the primary analysis based on the British EQ-5D, with societal costs, according to the friction cost method, the QALYs and costs for strategy 1 were less favourable than for strategies 2 and 3. Strategy 4 resulted in the highest number of QALYs, but at considerably higher costs: the cost-utility ratio of strategy 4 compared with the best alternative, strategy 3, was €130,000 per QALY, which is generally considered too high.

In the secondary analysis based on the Dutch EQ-5D, SF-6D and time trade-off (TTO), the QALY differences between strategies were smaller than for the British EQ-5D, therefore the cost-utility ratios of strategy 4 compared with strategy 3 were higher: €140,000; €250,000 and €320,000 per QALY, respectively.

Restricting costs to only health care (with QALYs based on the British EQ-5D), the cost-utility ratio of strategy 4 compared with strategy 3 was €190,000 per QALY.

The most crucial factor in the secondary analyses was the method used to value productivity costs. If productivity was valued according to the human capital method, then the costs and QALYs for strategies 1 and 2 were less favourable than for strategies 3 and 4. The cost-utility ratio of strategy 4 compared with strategy 3 was €22,000 per QALY, which was generally considered highly acceptable. It is an important establishment of the article that using the human capital method, the more favourable productivity costs almost completely compensated for the higher costs of the initial combination therapy with infliximab.

The study showed that initial combination therapy with infliximab resulted in significantly better quality of life than the other treatment strategies. Considering only health care costs, this improvement is obtained at costs that are generally considered too high, and initial

combination therapy with prednisone would be preferred. Depending to the extent to which productivity was valued, the costs of infliximab could be largely compensated by saving on productivity costs.

Kobelt et al., Sweden (2011) – etanercept[57]

In this article the cost-effectiveness of early biologic treatment, followed by dose-reduction in the case of remission is compared with standard treatment.[57] The economic model adapted was based on the combined effect of function and disease activity to estimate costs and utility of different treatment options and radiographic progression was incorporated as an effect on function. Regarding the results, the ICER for etanercept/MTX was €13,500 compared with MTX alone. As for sensitivity analyses, it was performed for the time horizon, the perspective, the discontinuation rate, the proportion of patients switching or returning to full dose and the utility adjustment in the biologics group. As for the results of sensitivity analyses, costs for the etanercept/MTX strategy were slightly higher, but associated with a QALY gain of 1 to 2.3. Results were most sensitive to the drop-out rate, the duration of treatment with reduced etanercept dose, time horizon and the perspective of the analysis. The utility adjustment did not change the results significantly. ICERs changed with varying certain assumptions:

- when 75 percent instead of 50 percent of drop-outs are switching to a biologic, the cost per QALY gained with etanercept/MTX decreases to €10,400 as costs in the MTX strategy increased proportionally more due to the higher underlying drop-out rate
- if the drop-out rate increased in both groups, the cost per QALY for etanercept/MTX decreased, again due to a larger cost increase in the MTX strategy: with a double drop-out rate, the ICER decreased to €2,200.
- if failure to maintain remission was double, or if dose reduction was only possible during the clinical trial period, the ICER for etanercept/MTX increased to €19,400.
- including only medical costs, the ICER increased to €34,000
- a longer time perspective (20 years) reduced the ICER to €8,200

The core point of the study was that the dose-reduction in the early RA may influence positively the cost-effectiveness of biologic treatment. The results indicated that a situation where a considerable proportion of patients achieved remission, dose-adjustments will increase the cost-effectiveness of treatment.

Schipper et al., The Netherlands (2011) – TNF-α inhibitors[98]

A Markov model was used to evaluate the cost-effectiveness of the following three strategies on 5-year horizon: starting MTX monotherapy, followed by the addition of leflunomide (LEF), followed by MTX with addition of anti-TNF; Strategy 2: start with MTX and LEF combination followed by MTX with anti-TNF; and Strategy 3: immediate start with MTX and anti-TNF. The analysis was performed following both a health care and societal perspective. Starting with a combination (MTX plus LEF or anti-TNF) was more costly than starting with MTX alone, the ICER for starting on anti-TNF vs. initially MTX was from the health-care perspective €138,028/QALY and from a societal perspective of €136,150/QALY over 5 years.

6.2.2.2 RA patients who failed synthetic DMARD therapy

Vera-Llonch et al., US (2008) – abatacept[121]

The cost-utility of abatacept treatment in women aged 55–64 years with moderately to severely active RA and inadequate response to MTX was analysed on a 10-year and lifetime horizon.[121] Abatacept plus methotrexate therapy was compared to methotrexate treatment, no other biological drugs were considered as alternative strategies. Efficacy data were retrieved from the abatacept phase III clinical trial (AIM). Abatacept therapy was assumed to result an improvement in the HAQ-DI in comparison with MTX alone. Patients with HAQ-DI improvements of 0.5 or greater at 6 months were assumed to continue to receive abatacept; those failing to achieve this level were assumed to discontinue treatment with a HAQ returning to a value equal to what it would have been in the absence of such treatment. All patients discontinuing abatacept (irrespective of reason) were assumed to continue to receive MTX. For patients receiving MTX only the HAQ-DI was assumed to increase by 0.065 annually to reflect disease progression. For patients receiving abatacept plus MTX the

estimated mean (SD) percentage HAQ-DI change at 3 months following therapy initiation was -30.2% (±36.1%); at 6 months, it was -35.2% (±37.6%). This clinical benefit was assumed to remain constant in those who continued abatacept, nevertheless an annual disease progression of 0.015 was applied. Only medical treatment costs were considered and both costs end utilities were estimated on predicted values of the HAQ. A discount rate of 3% was applied. Mortality risk was estimated based on age and the expected value of the HAQ-DI.

Over 10 yrs, the non-discounted QALY gain with abatacept was 1.2 per patient (4.6 vs. 3.4 for MTX) at an incremental (discounted) cost of $51,426 ($103,601 vs. $52,175, respectively); over a lifetime, corresponding figures were 2.0 QALYS (6.8 vs. 4.8) and $67,757 ($147,853 vs. $80,096). Cost-effectiveness was [mean (95% CI)] $47,910 ($44,641; $52,136) per QALY gained over 10 years and $43,041 ($39,070; $46,725) per QALY gained over a lifetime. The probability that abatacept would be cost-effective at a threshold of $50,000 per QALY was 0.80 over a 10 year time horizon, and 0.99 when a lifetime perspective was employed.

Sensitivity analysis was performed for different scenarios (e. g. no therapy discontinuation for lack of efficacy or other reasons; therapy discontinuation for lack of efficacy occurs at 3 months; variation of mortality related to HAQ; no mortality benefit with abatacept therapy; variation of annual HAQ increase; variation of the threshold for clinically meaningful improvement) confirming the robustness of the results (10-year: $40,190 to $70,209, lifetime: $37,551 to $60,106 per QALY).

Virkki et al., Finland (2008) – infliximab[122]

Cost-utiliy of infliximab was estimated in Finnish RA patients in a real-life clinical setting (n=297).[122] The median ICER of infliximab versus synthetic DMARD treatment was 51,884 €/QALY. The strength of this analysis is that real-life data were extensively used nevertheless methodological weaknesses hampers the results (e.g. no alternative biologicals were considered for the analysis).

Kobelt et al., Sweden (2009) - TNF-α inhibitors[58]

Kobelt used patient level data from a registry to feed a discrete event simulation model. They analysed the cost-utility of TNF inhibitor treatments in Sweden. The 10-year costs in the base

case amounted to USD336,000 (S.D.=USD 64,000) or €223,000, with a total of 4.4 QALYs. Over 5 years, the costs amounted to USD 208,000 or EUR 138,000 and QALYs to 2.5. The results were most sensitive to HAQ level at treatment start, but also to underlying disease progression, age, and disease duration. Starting treatment at a lower HAQ level (0.85) reduces costs by 10% and increases QALYs by 20%.

Sany et al., France (2009) – infliximab[95]

A cost–utility analysis of the annual costs was done with a comparison between the previous and the following year under infliximab treatment based on registry data, involving a cohort of 635 RA patients.[95] The analysis was performed from the health insurance coverage point of view however indirect costs were also considered. Before the use of infliximab, after 1 and 2 years, the mean annual cost per patient for the care of RA was €9,832, €27,723 and €46,704, respectively. In this analysis the incremental net benefit (INB) was used instead of ICER. INB is an indicator equivalent to the cost–effectiveness ratio. It is defined for a willingness to pay lambda by the formula INB(lambda)=lambda delta Effectiveness–delta Costs. INB(lambda)>0 means that, for the willingness to pay lambda, the cost–effectiveness ratio is perhaps acceptable by the society and will be so if the 95% CI is positive and lower than the acceptable threshold lambda (€45,000 in France). According to the analysis when it was expressed in QALYs, also for severe HAQ, lambda>€100,000.

Lekander et al., Sweden (2010) – infliximab[64]

The main feature of this study is that the assessment of cost-effectiveness of infliximab compared to nonbiological treatment based on real-world patient-level data.[64] These patient-level data were derived from the SRQ (Swedish Rheumatology Quality) Register. Such patient registries have several advantages:

- enable important complementary analyses of cost-effectiveness of TNF-use in RA
- represent real-world use compared with the more selective and controlled nature of the trial-based data
- using large patient cohorts from clinical practice ensures high external validity of the assessments

- disease-progression while on treatment can also be tracked over longer time compared with data from clinical trials which generally have shorter follow-up
- using registry data enable incorporation of real-world data on drug discontinuation patterns in the economic evaluation

On the other hand, where it was necessary, the data have been complemented with published data, including rate of natural disease progression, costs and utilities. For example, the comparator arm (natural progression without biological treatment) was based on published results from the ERAS study and not on STURE registry data which reflects the most important limitation to cost-effectiveness assessments based on real-world data.

Another particular characteristic of the model applied is that data on adverse events were included.

According to the STURE registry data, there was a change in treatment patterns over time, identifying a change to infliximab use earlier in the course of the disease in more recent years which was reflected both in shorter disease duration and lower baseline HAQ values. Based on disease duration at start of infliximab therapy, subgroups of patients in the data set with earlier stage RA and later stage RA were, therefore, analysed separately and compared with the base case, enabling a reflection of how the cost-effectiveness have been affected by this shift in treatment strategy.

Regarding the results, the base case analyses showed that the gain in QALYs associated with infliximab treatment was 1.019. Infliximab was also associated with an incremental cost of €23,264, resulting in an ICER of €22,830. According to the analyses of earlier- and later-stage RA, the ICER was lower for patients with earlier-stage RA and higher for patients with later-stage RA compared with the base case.

The sensitivity analyses conducted estimated the effects of a range of variables: adverse events, age at start of treatment, costs, discount rate, disease progression, drug costs, and mortality. In addition, both best- and worst-case scenario were performed. As for results, age at start of treatment initiation and the rate of natural disease progression had the largest effect on the ICER. The results ranged from €18,000 to €47,000. The best-case scenario resulted in an ICERs of €8,360 and the worst-case scenario €67,237.

The main surplus value of this analysis was the assessment based on real-world data. The ICERs of infliximab compared with natural progression and ICERs in all sensitivity analyses fell well below €65,000 per QALY which is a commonly referred threshold for cost-effectiveness in Sweden. A further important interpretation of the results is that treating patients with earlier- than later- stage RA was potentially most cost-effective.

Schulze et al., Germany (2009) – etanercept[100]

This article based on the TEMPO study which had shown that the combination of etanercept and MTX in the treatment of RA is superior to monotherapy.[100] It further suggested that remission of RA is a realistic treatment goal. Taking into consideration these establishments, the objective of the study was to demonstrate the sustainability of the combination for daily clinical practice taking economic aspects into account.

The main characteristics of the study in which it differs from the most ones:

- containing both cost-effectiveness (CEA) and cost utility (CUA) analyses
- besides HAQ applying a German instrument, namely Funktionsfragebogen Hannover (FFbH) to measure the functionality of patients

As for the results, the incremental cost-effectiveness ratio of the combination was €21,300 per life year in remission as compared with MTX alone. The incremental cost-utility ratio of the combination was €38,700 per QALY.

These results indicate that both health-economic parameters suggest adopting the combination therapy into daily clinical practice of RA patients.

Soini et al., Finland (2012)– adalimumab, etanercept, tocilizumab[106]

Different treatment sequences were compared in a hypothetical Finnish moderate to severe RA patients using a probabilistic microsimulation model in a lifetime scenario. Adalimumab + MTX, etanercept + MTX, or tocilizumab + MTX were used as first biologics followed by rituximab + MTX and infliximab + MTX and MTX alone was added as a further comparator. (The first-line biologic DMARD comparators included were the two established and reimbursed TNF inhibitors – the most used (adalimumab, ADA) and most affordable

(etanercept, ETA) – and a new option (tocilizumab, TOC). Important note: infliximab + MTX and rituximab + MTX were considered as second line biological therapies.).The resources were valued with Finnish unit costs (year 2010) from the healthcare payer perspective but additional analyses were carried out, including productivity losses. Biologic DMARDs significantly increase the QALYs gained when compared to MTX alone. Tocilizumab + MTX was more cost-effective than adalimumab + MTX or etanercept + MTX in comparison with MTX alone, and adalimumab + MTX was dominated by etanercept + MTX. The ICER with tocilizumab + MTX methotrexate was €18,957 (€17,057) compared to MTX alone. According to the cost-effectiveness efficiency frontier and cost-effectiveness acceptability frontier in Finland, tocilizumab + MTX should be considered before rituximab + MTX, infliximab + MTX, and basic supportive care.

Diamantopoulous et al., Italy (2012) – tocilizumab[32]

An individual patient simulation model was used assess the cost-utility of treatment sequences starting with tocilizumab or the most commonly prescribed biologics (etanercept, adalimumab, or infliximab) in Italy.[32] In the analysis strategy ETA – ADA – RTX -ABA – palliative was compared to TOC – ADA – RTX – ABA – palliative care strategy. Alternative analysis replaced etanercept with adalimumab or infliximab: ADA – ETA – RTX – ABA – palliative; INF – ETA – RTX ABA – palliative. Authors also analysed the cost-utility of adding TOC to standard-of-care: TOC – ETA – ADA – RTX – ABA – palliative. Other TNF-α blockers such as golimumab or certolizumab pegol were not considered in the analysis. The model applied lifetime horizon. Patient characteristics, treatment efficacy, and quality-of-life data were based on three phase 3 tocilizumab clinical trials (OPTION, TOWARD, LITHE). Only direct costs were considered. In the base-case analysis tocilizumab dominated standard of care. In the basecae analysis replacement of etanercept with tocilizumab reduces costs and realized more QALYs. Similar results were found if adalimumab was replaced, the ICER in case of infliximab replacement was €2,655/QALY. Adding tocilizumab to standard-of-care sequence resulted an ICER of €17,119/QALY. Tocilizumab was dominant in sensitivity analyses.

6.2.2.3 RA patients who failed at least one biologic DMARD therapy

Kielhorn et al., UK (2008) – rituximab[52]

Incremental cost-effectiveness of rituximab treatment was modelled on the lifetime horizon using a Markov model of 6-months cycles.[52] The analysis compared cost and outcomes of two treatment sequences, representing the current UK standard both with and without rituximab. The population characteristics matched those of the Randomised Evaluation of Long-term Efficacy of rituximab in RA (REFLEX) phase III randomised control trial. Five HAQ categories were established in the model and average cost for each category was estimated from the UK registry. Only direct medical costs were considered for the analysis. Utility data (health gain) were mapped from HAQ.

The model assumed that patients receive etanercept prior to entering the simulated treatment sequence, thus no further data on etanercept were presented.

In the primary analysis patients either follow the current standard treatment sequence of synthetic DMARDs reflecting real life clinical practice in the UK or an alternative sequence, which is identical, except for the introduction of rituximab:

- leflunomide, gold, cyclosporin, palliative care/methotrexate vs.

- rituximab+methotrexate, leflunomide, gold, cyclosporin, palliative care-methotrexate.

In the secondary analysis, switch between TNFα blocking agents is included:

- adalimumab+methotrexate, infliximab+methotrexate, leflunomide, gold, cyclosporin, palliative care/methotrexate vs.

- rituximab+methotrexate, adalimumab+methotrexate, infliximab+methotrexate, leflunomide, gold, cyclosporin, palliative care/methotrexate

Repeated courses of 2x1000 mg rituximab at every 9 months was considered, for all other drugs licences dose as per the EU label was used. (Infliximab: 3 mg/kg, average patient weight: 75 kg, no drug wastage or increase in dose was included in the calculation; adalimumab 40 mg every second week).

Patients enter the model and are allocated to either of the two treatment sequences. They are then exposed to the first treatment in the sequence and are allocated to one of the three responder groups (ACR 20–49, 50–69, 70+) or to the non-responder group. The mean drop in

HAQ for each of these groups was calculated from the rituximab phase III trial (REFLEX). The HAQ score is assumed to drop by 0.1 for non-responders, 0.45 for ACR20–49, 0.85 for ACR50–69 and 1.11 for ACR70+ responders. While on treatment, patient HAQ scores are assumed to progress by 0.017 during each model cycle. For patients on palliative care a HAQ progression of 0.065 was assumed. Once treatment stops, the entire initial gain in HAQ is assumed to be lost instantly (100% rebound effect). Time on treatment was applied from a study by Barton et al.[11] assuming 4.25 years for all bDMARDs (including rituximab) apart from infliximab where a higher drop-out was assumed (2.46 years). Regarding the non-biological DMARDs treatments, duration was 1.7 years for cyclosporin, 3.85 years for gold and 4.1 years for leflunomide. Mortalities derived from the life-table were adjusted to the individual's HAQ score (1.33 / unit HAQ). A discount rate of 3.5% was applied. Total discounted QALYs were 3.051 and 2.324 for the rituximab arm and the standard of care arm, respectively, resulting in an incremental QALY gain of 0.727 in the primary analysis. In the secondary analysis a lower QALY gain was observed (0.526). The incremental cost-effectiveness ratio (ICER) was £11 749 and £6103 per QALY in the primary and secondary analysis, respectively. In the sensitivity analysis significant variability was observed in changes to rituximab dosing re-treatment (from 9 months to 6 months) and when changing the HAQ long-term progression. Variability was also observed when baseline age is increased. However when measuring the cost-effectiveness acceptability, the model estimates that there is an 89% probability of rituximab being cost-effective at a threshold of £30,000.

Vera-Llonch et al., US (2008) – abatacept[121]

Cost-utility of abatacept compared to synthetic DMARD treatment was assessed using a simulation model to depict progression of disability (HAQ) in women with moderately to severely active RA and inadequate response to anti-TNF.[121] Outcomes and costs were simulated alternatively over 10 years and a lifetime for a hypothetical cohort of 1,000 women between the ages of 55 and 64 years. At model entry, patients were assumed to receive either oral disease modifying antirheumatic drugs (DMARD) only or oral DMARD plus abatacept. (At the time the study was conducted, efficacy data in this patient population were available for abatacept only.) Efficacy data were retrieved from the ATTAIN clinical trial. For patients receiving oral DMARD only, the HAQ-DI was assumed to increase by 0.065 annually to reflect disease progression. Patients with HAQ improvements of –0.50 or greater at 6 months were assumed to continue to receive abatacept; those failing to achieve this level of clinical

benefit were assumed to discontinue treatment. Patients also were assumed to possibly discontinue abatacept for other reasons (adverse events). All patients discontinuing abatacept were assumed to continue to receive stable doses of oral synthetic DMARD. Authors did not consider switching from abatacept to another biologic DMARD as there are no data on the efficacy of the latter agents given prior failure with abatacept. For patients discontinuing abatacept, the HAQ-DI was assumed to return to a value equal to what it would have been in the absence of such treatment. The QALY gain with abatacept compared to synthetic DMARD was 1.0 QALY (undiscounted) per patient over 10 years and 1.6 QALY over a lifetime. Incremental cost-effectiveness of abatacept (2006 US$) over a 10-year time horizon was estimated to be [mean (95% CI)] $50,576 ($47,056, $54,944) per QALY gained (3% discount rate used for both costs and effectiveness). On a lifetime basis, cost-effectiveness was $45,979 ($42,678, $49,932) per QALY gained. Findings were robust in sensitivity analyses.

Lindgren et al., Sweden (2009) – rituximab[66]

Lindgren et al. estimated the cost-effectiveness of rituximab in RA patients not responding adequately to the first TNF-α inhibitor using a model constructed to predict resource consumption and health outcomes in a population-based registry of biological treatments in Southern Sweden.[66] Resource consumption was based on a regular population-based survey of patients in Southern Sweden. Rituximab was incorporated as second line treatment, using effectiveness from a clinical trial (REFLEX and it was thus compared to the mix of second line biologics used in SSATG. Total costs in the rituximab strategy are estimated at €401,100 compared with €403,000 in the TNF-inhibitor arm. Total QALYs are 5.98 and 5.78, respectively. In terms if ICER rituximab therapy was dominant strategy and findings were found to be robust in extensive sensitivity analysis.

Brodszky et al., Hungary (2010) - rituximab

Cost-utility of rituximab (RTX) versus palliative care (synthetic DMARD) was modelled on a lifetime horizon in Hungary.[23] Two scenarios were applied: 1 course of RTX treatment (2 infusions) and 3-year RTX therapy. Baseline patient characteristics were equivalent to the patient population of the REFLEX rituximab trial (moderate and severe RA, who have failed DMARDs and at least one TNF-α inhibitor) and efficacy data were retrieved from this same

trial. Linear regression between HAQ and EQ-5D from a previous Hungarian survey was used to generate utility inputs. Official price lists were used for cost calculation and costs not directly connected with RTX treatment were estimated according to HAQ level, based on a Hungarian survey. Additionally a cost-minimization analysis was also performed to compare RTX treatment with switching from one TNF-α inhibitor to another. One course of rituximab treatment resulted an ICER of -31,140 €/QALY from societal perspective and 38,763 €/QALY from health care payer perspective. Results for repeated courses of rituximab were 11,234 €/QALY and 13,400 €/QALY, respectively.

Hallinen et al., Finland (2010)[42]

The aim of this study was to evaluate the cost-utility of different treatment strategies after treatment failure with one TNF-inhibitor in a Finnish setting.[42] Initially, the patients received either best supportive care (BSC) or one of the following treatments before BSC: adalimumab (ADA), abatacept (ABA), etanercept (ETA), infliximab (INF) or rituximab (RTX). Further treatments were added to the most cost-effective strategy in a stepwise manner. Rituximab and abatacept was considered as an option for those RA patients who did not tolerate or who did not get an adequate response to other treatments, including at least one TNF-inhibitor therapy. Regarding the results, the most efficient strategy is to use RTX+MTX→BSC or, if the WTP of €37,013 per QALY gained is not too much, RTX+MTX→INFL+MTX→BSC treatment strategies after TNF-inhibitor failure. In detail:

- adding a second biologic treatment after TNF-inhibitor failure increased the average treatment failure costs by €16,843-41,866 and gave 0.46-0.70 additional QALYs compared with BSC alone, depending on which biologic treatment was chosen. The most cost-effective choice was RTX+MTX with an ICER of €30 248 per QALY gained, which was lower than those of either INF+MTX (€36,121), ETA+MTX (€50,372), ADA+MTX (€50,941) or ABA+MTX (€67,003). Treatment with RTX+MTX dominated ETA+MTX, ADA+MTX and ABA+MTX, as it was less costly and more effective. Compared with INF+MTX, the cost of an additional QALY with RTX+MTX was €18,585.
- when a third biologic treatment was added after RTX+MTX, the average treatment costs increased further by €14,024-35,414 and resulted in 0.38-0.52 additional QALYs, depending on which biologic treatment came next. Compared with treatment

with RTX+MTX (→BSC), the ICERs of adding biologic treatment ranged from €37,013 (INF+MTX) to €68,100 (ABA+MTX) per QALY gained. Compared with giving INF,+MTX as the third biologic treatment, an additional QALY with ADA+MTX, ETA+MTX and ABA+MTX cost €260,197, €145,658 and €151,562, respectively.

- in case of a fourth biologic treatment was added after INF+MTX, the average treatment costs increased further by €20,595-34,547 and 0.38-0.49 additional QALYs were gained. Compared with treatment with RTX+MTX→INF+MTX→BSC, the additional QALY with ETA+MTX costed €54,836, with ADA+MTX €54,701 and with ABA+MTX €70,616. Compared with ETA+MTX and ADA+MTX, an additional QALY with ABA+MTX costs €158,411 and €123,755, respectively.

The study showed that treatment with rituximab was a cost-effective treatment strategy in Finland.

Merkesdal et al., Germany (2010) – TNF-α inhibitors, rituximab[76]

This study investigated the cost-effectiveness ratios of either (1) rituximab or (2) a TNF-α inhibiting agent as second line biological treatment in patients with active RA and an inadequate response to etanercept therapy.[76] The study differs from most of the cost-effectiveness analyses related to RA in several points.

- objective: while most economic evaluations focus on the cost effectiveness of TNF-inhibitors as (1) first line biological therapy after failure of DMARDS, or (2) first line therapy in early RA in comparison with MTX therapy, this cost-effectiveness analysis focused on second-line biological therapy comparing biological options after failure of TNF-inhibitors
- sensitivity analysis: uncertainties addressed by extensive sensitivity analysis, included not only the important input parameters for the model but also the methods used to derive these key parameters
- effectiveness evidence: the treatment sequence applied for the German treatment line was based on expert opinion. The employment of expert opinions in fields where superior evidence is missing is a common and accepted tool for the development of economic models

Regarding the results, the ICER of rituximab compared to the standard sequence amounted to €24,517 per QALY focussing on direct medical costs.

The inclusion of indirect costs in both treatment sequences showed higher cost estimates of €266,063 and €274,901. The incremental QALY gain was 0.57. This gave an ICER of €15,565 per QALY.

The inclusion of indirect costs reflects the cost-saving potential of highly effective drugs on long-term outcomes such as work-productivity or work-disability rates. This is an important issue for the demonstration of the real value for money of an expensive but effective treatment option. The economic impact of these positive long-term effects in rituximab treatment became obvious when comparing the ICERs when productivity costs are either included or not (€13,922 vs €8,836), indicating a drop of incremental costs of about 40% due to effects on indirect costs.

Malottki et al., UK (2011) - adalimumab, etanercept, infliximab, rituximab and abatacept[70]

Malottki et al. conducted a systematic literature search in 2009 for RCTs, cost-effectiveness and cost-utility studies of adalimumab, etanercept, infliximab, rituximab and abatacept treatment in RA patients who failed at least one biological therapy. They identified three cost-utility studies which were identical to literature search was closed at those captured by our search.[52, 66, 121] They performed an independent economic assessment as well.

One course of RTX results in 0.144 QALY gain compared with palliative treatment (non-biological DMARD) in lifetime horizon, incremental direct and total costs are 5,582 € and 4,494 €, respectively, resulting an ICER of – 31,140 €/QALY from societal perspective and 38,763 € from health care payer perspective. Three-year treatment with RTX provided a gain of 0.511 QALY at an incremental direct and total costs of 13,400 € and 11,234 €, respectively, the ICER was 26,223 €/QALY from societal and 21,980 €/QALY from health care payer perspective. Cost-minimization proved that that RTX dominates TNF-α inhibitor for patients who have failed 1 previous TNF-α inhibitor therapy.

Benucci et al., Italy (2011)[14]

This study focused on the cost-effectiveness of rituximab treatment based on follow-up data of 32 RA patients in Italy.[14] Only direct costs were considered in the analysis. After 1 year of treatment the observed ICER on 28 patients was €23,696/QALY. The ICER was more favourable if rituximab was applied as second line compared to third line treatment.

6.2.3 Summary of the main findings of the new literature search

6.2.3.1 DMARD naive RA patients

Evidences are summed in Table 6. The four articles involving DMARD naive RA patients assessed the cost-utility of etanercept, infliximab and adalimumab as first line therapies. Two of them were performed in The Netherlands, one in the US and one in Sweden. Among the studies 1 applied payers', 2 societal perspective and 1 both. All of them applied discount rates (3% n=3; 4% n=1) both for the effects and costs. Efficacy data were derived from different sources including registry and RCT data (e.g. BeSt trial, COMET trial) but also assumptions were made i.e. efficacy of TNF-α inhibitors was considered from patients with DMARD experience in one of the Dutch analysis. All the four were modelling studies (2 individual sampling, 2 Markov models), the time horizon was 2 years (n=1), 5 years (n=1) and lifetime (n=2). Utilities were obtained by the EQ-5D (n=3) and HUI (n=1) and one study performed sensitivity analysis for other utility measurements as well. In the US, the ICER of adalimumab sequence dominated the etanercept and infliximab sequences. In The Netherlands the ICER of strategy 4 (initial combination with infliximab) compared with strategy 3 (initial combination with prednison) was €130,000/QALY, and in the other Dutch study the ICER of anti-TNF strategy compared with the MTX strategy was €136,207/QALY from the societal perspective. In Sweden early etanercept therapy was compared to MTX alone, no other biologicals were considered in the analysis. The ICER for the biologic strategy was €13,518/QALY if dose adjustment was allowed for patients in remission.

6.2.3.2 RA patients who failed at least one traditional DMARD therapy

The summary of the evidences is given in Table 7. Eight analyses estimated the cost-utility of biologicals in RA patients who failed at least one traditional DMARD therapy. The studies were performed in Sweden (n=2), Finland (n=2) US, (n=1), France (n=1), Italy (n=1) and Germany (n=1). The health care payer's perspective was used in the majority of the studies (n=5). Besides the TNF-α inhibitors abatacept and tocilizumab were also analysed. Six models and two observational studies were applied and data sources of efficacy were not restricted only to RCTs but real life data were also incorporated in many analyses. Seven studies derived EQ-5D utilities from HAQ (regression) and only one in Sweden used survey results of a registry. Most studies used lifetime horizon but alternative assessments were often performed in sensitivity analyses. In general, the ICER for TNF- α inhibitors was within the acceptable range. Studies suggest that tocilizumab might be beneficial as well, abatacept resulted an ICER $47,910 on 10-year horizon when compared to MTX therapy (no other alternatives were considered).

6.2.3.3 RA patients who failed at least one biological DMARD

The summary of evidences are presented in Table 8.Eight studies analysed the cost-utility of biologicals for RA patients whom has already failed at least one biological DMARD therapy. The studies were performed in the UK (n=2), US (n=1), Sweden (n=1), Finland (n=1), Germany (n=1), Italy (n=1), Hungary (n=1). Rituximab and abatacept treatments were compared to traditional DMARD and TNF-α inhibitor sequences. With the exception of a 1-year observational study in Italy, all evaluations applied modelling approach on a lifetime horizon, data for effectiveness were retrieved from RCTs. Societal perspective was used only in three studies. Rituximab seems to be dominant strategy compared to TNF-α inhibitor sequences. The ICER of abatacept compared to MTX therapy was $50,576/QALY on a 10-year horizon and $45,979/QALY on lifetime horizon in the US.

6.2.4 Potentially useful articles with English abstract

Prokes M.,Czeh Republic (2009) [Article in Czech]– adalimumab, infliximab, etanercept[89]

A comparison of effectiveness of adalimumab, infliximab and etanercept in the treatment of RA was made and cost-effectiveness of each TNF antagonist for Czech Republic was performed.[89] The prices of therapy of all three TNF antagonists are similar in the first year of treatment of patients with average weight, in the second year the price of infliximab is lower, but only in the case of patients where the doses do not reach 4 amp. of infliximab. Clinical effectiveness was evaluated in DAS28 and HAQ units. Cost-effectiveness of all TNF antagonists was similar, when 2 amp. of infliximab per dose physician considered sufficient, but when patients were given higher doses of infliximab the trend to lower cost-effectiveness of infliximab compared to adalimumab and etanercept was observed.

Belevitin AB et al, Russia (2010) [Article in Russian][12]

According to Medline parameters of the article authors discuss the costs and benefits of adalimumab in RA and the methods of economic assessment of advisability of modern biological medication usage in military medicine.[12]

Benucci et al., Italy (2009) [full text not available][13]

The objective of this study is to perform a cost-effective analysis of 86 patients with RA in therapy with adalimumab 40 mg every other week and etanercept 50 mg/week for two years in a population of patients observed in clinical practice. Incremental costs and QALYs gains are calculated compared with baseline, assuming that without biologic treatment patients would remain at the baseline level through the year. The results after two years showed an ICER for the adalimumab group €42,521.13/QALY and for the etanercept group €39,171.76/QALY.

6.3 Discussion, conclusions

There is an increasing demand for cost-effectiveness data in the decision making process across Europe. Cost–effectiveness analyses are always comparative and incremental, that is, they permit an insight to the benefits, costs and the potential savings of a product compared with other pharmaceuticals and/or treatment, optimally in a reliable, reproducible, and verifiable way. However, to make the cost-effectiveness analysis useful for decisions on resource allocation, the health benefit must be expressed with a measure that is comparable across diseases. Cost-utility analysis expresses the incremental benefits of a treatment compared to others in ”quality adjusted life year” (QALY) where the ”Q” include information on the utility of a health status from a societal point of view. The incremental cost-utility ratio (ICUR, but often called simply as incremental cost-effectiveness ratio - ICER) presents then the incremental expenditures needed to achieve 1 QALY gain. The lower the ratio of a cost per QALY, the most cost-effective the intervention is said to be.

Even though there is no theoretical or empirical basis for it, ICER values ranging from $50,000 to $100,000 / QALY are sometimes used as a threshold in the United States, where as in the UK, NICE has adopted a cost–effectiveness threshold range of £20,000 to £30,000 / QALY gained.[80] Although in several European countries (including Hungary and many others from the Eastern and Central region) there is not a well-defined threshold for reimbursement decisions, the ICER ratio is often used as basis for the evaluation of new technologies.

Therefore, in our current report we focussed on cost-utility analyses of biological therapies in RA. Our systematic literature review revealed 36 cost-utility studies. The majority (n=19) evaluated biological treatment for RA patients who have already failed at least one traditional DMARD therapy, eight considered those who have failed at least one biological drug. However the number of studies involving DMARD naive RA patients was rather substantial as well (n=9).

There are several key steps when performing and interpreting health economic reports. These include (1) defining perspective and time horizon, (2) collecting data on healthcare utilization, (3) costing healthcare resources,(4) analysing data on utilization and cost, (5) defining and measuring health effects, (6) adjusting costs and effects for inflation and discounting, (7) and evaluating uncertainty.[80] There was extensive methodological heterogeneity across the 36 selected health economic evaluations. Economic perspectives included societal and payer,

some studies presented results for both. The majority applied model-based analytic approach but some relied on short (1 or 2 years) observational data. All of the studies considered direct costs but indirect costs were ignored by many evaluations. Data from randomized controlled trials were used the most frequently to assess effectiveness but in some cases (especially in the latest analysis) findings from registries were also incorporated. Real-world data might refine the results of RCT based economic evaluations and be more generalizable to the field. However at the same time their outputs are more difficult to interpret and the internal validity of the findings is more limited.

The quality of reporting is crucial in health economic publications since usually neither the model itself nor the inputs (e.g. patient level data from RCTs or cohorts) are available. Hence the analysis is not reproducible for outsiders and critical appraisals have to rely on the reported data. The checklist developed by Drummond et al. is widely used for the quality assessment of health economic papers.[34] Applying these criteria on the 36 selected publications we found that reporting practices often failed to present key data appropriately. Authors commonly missed to describe methods for identifying, selecting, and synthesizing data for key model parameters and also study design was not clearly described in many publications. Important details which might have significant impact on the results (e.g. dose escalation) were frequently missing from the description.

Considering the above mentioned variability and weaknesses of the methods definitive conclusions are difficult to make regarding the cost-utility of biologicals in RA. There is mixed evidence of cost-effectiveness in selected populations. For instance, the ICER of infliximab+methotrexate therapy for RA patients who failed methotrexate monotherapy varied between 6,451-91,484 CAN$/QALY in a Canadian review.[119] Not only the time horizon and discounting were deterministic but also different utility measures (EQ-5D, HUI-2, HUI-3, SF-6D) resulted quite diverse ICERs (37,209 – 80,620 CAN$/QALY) even if the same perspective was applied.[72]

However for the current health technology assessment the basic questions are whether the available literature results are relevant to Central and Eastern European countries (namely Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovak Republic), and how to

transfer them to support local policy making, financing and reimbursement decisions and professional guidelines.

Most of the cost-utility analyses were performed in the US (n=8) and Northern Europe (Sweden n=7, Finland n=3), but countries from Western Europe also contributed with numerous evaluations (UK n=6, The Netherlands n=3, Germany n=2, Italy n=2, France n=1). Canada and Japan had 2 and 1, respectively. Only one publication from Hungary was available in English.

These countries differ considerably from Central and Eastern European countries in GDP per capita, health and social care systems, demography, morbidity, health status of the given population in question (RA), comparator medications, standard practice, prescription behaviours of the doctors, reimbursement mechanisms of medications and financing of health care institutions, price level, unit costs, direct and indirect costs. Thus the transferability[i] of these health economic results to jurisdictions of Central and Eastern Europe is rather limited. Furthermore, there are noticeable limitations in terms of HTA capacity (number of professionals and budget to generate new country specific HTA results) in the Central and Eastern European region. Hence it is essential to find out how can these published results be made more transferable and more useful. Managed transferability is crucial for sustainable financing of biological medications.

For that purpose a wide spectrum of deterministic factors has to be analysed, such as country-specific RA guidelines (both professional and financing), financing mechanisms, patient data, financing incentives, access to health care facilities where biologicals provided to RA patients. Some important questions will be answered by this HTA report. However, we will presumably face the problem of lack or at least shortage of information. To bridge this gap and to achieve reliable data we have to collect as many reliable local data as possible and develop a model which is able to represent the environment where it is used (country-specific characteristics) and which also allows investigating the effect of different hypotheses and scenarios on a number of outcomes. Conference abstracts reflect an increasing activity in

[i]The ISPOR Task Force's working definitions were that economic evaluations were *generalizable* if they applied, without adjustment, to other settings. On the other hand, data were *transferable* if they *could be adapted* to apply to other settings. Also, the generic term 'jurisdiction' was used to mean any setting where there is a need for local estimates of cost-effectiveness. Often this would be a country, but could also be a region within a country, or a particular payer, such as a health plan. However, when referring to a particular study, more specific terms like 'country' or 'clinical center' are used if they help in the explanation of the study's methods (Drummond 2009, Gulácsi 2005)

many countries and it is highly probable that further studies can be captured by reviewing local papers and submission dossiers. For instance in Hungary, several cost-of-illness studies, partial and full HTA reports are available in Hungarian often with short English abstract.[20-22, 24, 25, 41, 69, 86, 87] These sources might offer important inputs for country-specific health economic modelling and provide relevant information about the reimbursement practice in a specific country.

Table 6 Methotrexate naive early RA patients - summary of cost-utility evidence identified

Data	Davies et al., USA (2009)[30]	Ven den Hout et al., The Netherlands (2009)[116]	Kobelt et al., Sweden (2011)[57]	Schipper et al., The Netherlands (2011)[98]
Perspective	payer	societal	societal	health care; societal
Comparators	adalimumab+MTX, etanercept, infliximab+MTX, adalimumab+MTX/etanercept and palliative care (DMARD)	sequental monotherapy, step-up combination therapy, initial combination therapy with prednisone and initial combination therapy with infliximab (BeSt trial)	etanercept+MTX vs. MTX	MTX – MTX+LEF – MTX+anti-TNF; MTX+LEF – MTX+anti-TNF; immediate start with MTX+anti-TNF
Model structure	Individual patient simulation model based on the model by Bansback et al.[9], five alternative sequences of therapies, lifetime horizon, 6 months cycles, responses according to ACR and associated HAQ score..	Individual sampling model	Markov model, 6 month cycles, lifetime horizon; adapted to early RA and transformation of the model to accommodate dose reductions and treatment switches.	Markov model, 3-month cycles, 5-year horizon, health states by disease activity
Patient inputs	patient characteristics from the PREMIER trial	baseline characteristics: 508 patients with recent onset active RA from 20 Dutch medical centers were enrolled	Patients with the characteristics of the total population enrolled in COMET	registry
Sources of effectiveness evidence	Short-term trial data (PREMIER, ASPIRE and ERA) were used to determine the response rates and HAQ	Effectiveness from BeSt study	COMET trial. Discontinuation rates: South Swedish Biologics Registry (SSATG) to determine HAQ and DAS28	registry, efficacy data of anti-TNF were derived from patients with prior DMARD use

Data	Davies et al., USA (2009)[30]	Ven den Hout et al., The Netherlands (2009)[116]	Kobelt et al., Sweden (2011)[57]	Schipper et al., The Netherlands (2011)[98]
Sources of cost data	HAQ profiles were used to calculate direct and indirect costs. Monitoring and administration costs were calculated based on clinicians' assessments. To measure other direct medical costs (e.g ., physician visits, hospitalizations) a regression equation based in HAQ scores was used. Productivity costs were based on the proportion of annual average earnings lost associated with worsening HAQ scores	Costs reported by the patients were used. Besides, published costs or market costs were applied. In the primary analysis the friction cost method, in the secondary analysis the human capital method was used.	Population-based survey including direct costs and indirect costs (productivity losses in the Malmö area, combined with early retirement data for a more urban population in Stockholm area)	related to disease activity states (from a 48-week multicentre trial)
Utilities	4 adalimumab trials were used to estimate utilities. HAQ scores were used to calculate utility values on a scale of 0 to 1 using a regression equation derived from HUI-3 utility scores. Patients' utility scores were modelled to decline by 0,28 for each one-unit increase in HAQ score	The British and Dutch EQ-5D utilities and the Short-Form 6D utility were calculated from EQ-5D and SF-36 questionnaires, respectively. Time-trade-Off method was used	Utilities (EQ-5D) were taken from the same observational study in Malmö	related to disease activity states (EQ-5D data from a survey)
Discount rate	3.0%	3.0%	3.0%	4.0%

Data	Davies et al., USA (2009)[30]	Ven den Hout et al., The Netherlands (2009)[116]	Kobelt et al., Sweden (2011)[57]	Schipper et al., The Netherlands (2011)[98]
Base case results	adalimumab+MTX/etanercept of 19,663 US$/QALY compared with adalimumab as sole TNF-antagonist and of 23,377 US$/QALY for adalimumab+MTX compared with the etanercept sequence. The sequences of etanercept and infliximab+MTX were extendedly dominated.	Primary analysis: based on the British EQ-5D, QALY was 1,41 for strategy 4 (initial combination with infliximab) at a cost of €32,403. The ICER of strategy 4 compared with strategy 3 was €130,000. Secondary analysis: based on the Dutch EQ-5D, SF-6D and TTO cost-utility ratios of strategy 4 compared with strategy 3 were €140,000; €250,000 and €320,000 per QALY, respectively. With human capital method the cost-utility ratio of strategy 4 compared with strategy 3 was €22,000 per QALY	Incremental QALY was 1,25 and incremental cost was €15,546 for etanercept+MTX. This gives an ICER for this biologic strategy of €13,518.	anti-TNF strategy compared with the MTX strategy from the health-care perspective €138,056/QALY, €136,207/QALY from the societal perspective
Key sensitivity analysis	ICER was sensitive to many of the changes in parameters: DMARD withdrawal rate, HAQ progression on anti-TNF, HAQ progression response, age, direct costs, mortality and utility	-	Results were sensitive to the drop-out rate, the duration of treatment with reduced ETA-dose, time horizon and the perspective of the analysis	If estimate of 30% of the DMARD-naive patients achieving remission with anti-TNF was applied: healthcare perspective €116,598/QALY, societal perspective €114,982/QALY

LEF= leflunomide, CYC= cyclosporine, MTX=methotrexate, RTX= rituximab;nbDMARD=non-biological Disease Modifying Antirheumatic Drug

Table 7 RA patients who failed at least one synthetic DMARD therapy - summary of cost-utility evidence identified

Data	Vera-Llonch et al., US (2008)[121]	Virkki et al., Finland (2008)[122]	Kobelt et al., Sweden (2009)[58]	Sany et al., France (2009)[95]	Lekander et al., Sweden (2010)[64]	Schulze-Koops et al., Germany (2009)[100]	Soini et al., Finland (2012)[106]	Diamantopoulos et al., Italy (2012)[32]
Perspective	third party payer	healthcare payer	societal	health insurance coverage	societal	societal	healthcare payer	National Health Service
Comparators	MTX versus MTX+abatacept (<60 kg:500 mg/vial; 60-100 kg: 750 mg/vial; >100 kg: 1 g)	infliximab vs. traditional DMARD	TNF blockers	before infliximab treatment compared to results after 1st and 2nd year of infliximab treatment	infliximab vs. no biological treatment (natural progression)	etanercept+MTX vs. MTX	adalimumab+MTX, etanercept+MTX, or tocilizumab+MTX were used as first biologics followed by rituximab+MTX and infliximab+MTX; supportive care (MTX)	tocilizumab Basecase: ETA – ADA – RTX - ABA – palliative vs. TOC – ADA – RTX – ABA – palliative care; Alternatives: ADA – ETA – RTX – ABA – palliative; INF – ETA – RTX ABA – palliative; adding TOC to standard-of-care: TOC – ETA – ADA – RTX – ABA – palliative
Model structure	simulation model, horizon: 10 yrs and lifetime; 3-months cycles, simulation of 1000 patients	real life data, assumption for patients without inflximab therapy	discrete event simulation, 5-year and 10-year horizon	analysis of real world data	Markov model with five health state (HAQ) categories each with two DAS28 states	Monte-Carlo-Markov-Chain stimulation, 5 HAQ states.	individual sampling model, 6 months cycles, lifetime horizon	individual patient simulation model, 6-month cycles, lifetime horizon

Data	Vera-Llonch et al., US (2008)[121]	Virkki et al., Finland (2008)[122]	Kobelt et al., Sweden (2009)[58]	Sany et al., France (2009)[95]	Lekander et al., Sweden (2010)[64]	Schulze-Koops et al., Germany (2009)[100]	Soini et al., Finland (2012)[106]	Diamantopoulos et al., Italy (2012)[32]
Patient inputs	women aged 55-64 years with moderate to severe RA, inadequate response to MTX	297 patients, mean age 51 yrs, 69% female, mean disease duration 12 years, HAQ 1,33	from a registry	mean age at entry 53.4 SD11.8 years, median DAS28 5.82 (5.15–6.56), NSAID treatment 90%, MTX 98.7%.	Individual sampling model using real-world patient -level data from the Stockholm TNF-alfa follow-up registry (STURE) n= 637, 1999 and 2008. 2 subgroups: were: patients with earlier- and late-stage RA	Individual sampling model using real-world patient -level data from the TEMPO study. 686 patients with active RA, mean disease duration >6 years.	moderate-sever RA, mean 52.5 years old, HAQ 1.51 at the baseline, weight 73 kg; 18% men	equivalent to baseline characteristics of tocilizumab trials' samples
Sources of effectiveness evidence	AIM trial	follow-up results; patients without infliximab were assumed to progress a.a31 HAQ/year	registry	registry; dose escalation of infliximab was considered	STURE registry, the comparator arm (nonbiological treatment): ERAS study	TEMPO trial	mixed treatment comparison of bDMARD trials	tocilizumab: three phase III trials, mixed treatment comparison for the therapy sequences

Data	Vera-Llonch et al., US (2008)[121]	Virkki et al., Finland (2008)[122]	Kobelt et al., Sweden (2009)[58]	Sany et al., France (2009)[95]	Lekander et al., Sweden (2010)[64]	Schulze-Koops et al., Germany (2009)[100]	Soini et al., Finland (2012)[106]	Diamantopoulos et al., Italy (2012)[32]
Sources of cost data	medical treatment costs	direct costs, official price lists; dose escaslation of infliximab was considered	official price lists; cost of biological treatment was estimated based on three parameters: actual usage, dose of each of the agents, and adverse events; other costs were obtained from a survey and related to HAQ	official price lists, data obtained from patient self-questionnaire	The direct and indirect costs were based on an empirical study by Kobelt et al., where costs were stratified by functional status based on Swedish registry data. The cost for added life-years were also estimated derived from Ekman et al.	Costs: German database. Indirect costs were calculated using the human capital approach	(sensitivity analysis included productivity loss as well)	drugs: official prices, other direct costs: Italian survey
Utilities	derived from HAQ (range: 0.86±0.16 – 0.03±0.33)	derived from HAQ (HAQ was measured int he follow up)	directly from a registry	derived from HAQ: EQ-5D=0.862–0.327*HAQ	Utilities were derived from an empirical study by Kobelt et al. and based on the current HAQ state and by disease activity	The instruments of HAQ and FFbH were used to generate utilities	derived from HAQ: EQ5D=0.82-0.11*HAQ-0.07*(HAQ*HAQ)	derived from HAQ: EQ-5D = 0.82 – 0.11 x HAQ - 0.07 x HAQ^2
Discount rate	3.0%	not applied	3.0%	not applied	3.0%	applied but not specified	3.0%	3.0%

Data	Vera-Llonch et al., US (2008)[121]	Virkki et al., Finland (2008)[122]	Kobelt et al., Sweden (2009)[58]	Sany et al., France (2009)[95]	Lekander et al., Sweden (2010)[64]	Schulze-Koops et al., Germany (2009)[100]	Soini et al., Finland (2012)[106]	Diamantopoulos et al., Italy (2012)[32]
Base case results	10-year horizon: $47 910 ($44 641, $52 136) / QALY; lifetime horizon: $43 041 ($39 070, $46 725) / QALY	median ICER 51,884 Euro/QALY	5-year horizon: cost EUR 138,000 and 2.5 QALY gain. 10-year horizon: cost EUR 223,000 and 4.4 QALY gain.	QALY gain total sample: 0.15 Incremental net benefit (INB): The INB was, in the total sample significantly positive >249 663.	Infliximab: QALYs 1,019, costs €190,089. Non-biological: costs €166,824. ICER of infliximab vs. non-biological therapy: €22,830/QALY.	MTX: QALYs 1017,1, costs €162,520,668. Etanercept+MTX: QALYs 2119,6, costs €206,163,041. ICER etanercept+MTX vs. MTX: € 39,585.	Tocilizumab was more cost-effective than etanercept and adalimumab in comparison with MTX alone (and both etanercept and tocilizumab dominated adalimumab (tocilizumab+MTX vs. MTX €17,057)	Tocilizumab dominates standard-of-care, also if ETA was replaced with adalimumab, but for INF replacement the ICER was €2,655. Adding TOC to standard-of-care: ICER 17,119/QALY.
Key sensitivity analysis	10-year: $40 190 to $70 209 / QALY; $37 551 to $60 106 QALY	(n=79 (35%)of the patients with QALY gain had an ICER of ≤40,000 Euro/QALY)	initiating biological therapy at shorter disease duration is more beneficial (higher gain at a lower cost).	Subgroups with higher HAQ result more beneficial results.	ICER was sensitive to many of the changes in parameters, in particular age at start of treatment initiation and the rate of natural disease progression	Results were sensitive to cost of etanercept, cost of acquired disability, the probability of withdrawals, the discount rate of costs and discount rate of effects	The modelling assumptions only had a small impact on the relative results.	Tocilizumab dominant.

Table 8 RA patients who failed at least one biologic DMARD therapy - summary of cost-utility evidence identified

Data	Kielhorn et al., UK (2008)[52]	Vera-Llonch et al., US (2008)[121]	Lindgren et al., Sweden (2009)[66]	Brodszky et al., Hungary (2010)[23]	Hallinen et al., Finland (2010)[42]	Merkesdal et al., Germany (2010)[76]	Malottki et al., UK (2011)[70]	Benucci et al., Italy (2011)[14]
Perspective	National Health Service (NHS)	third party payer	societal	society (alternative analysis: health care payer)	societal perspective	health care payer	National Health Service (NHS)	not stated (drug costs considered)
Comparators	rituximab vs. therapy sequences: Scenario A: LEF, gold, CYC, palliative care; Scenario B: ADA+MTX, INF+MTX, LEF, gold, CYC, palliative care; compared to: RTX+MTX (every 9 months) included in the sequence	abatacept+MTX vs. MTX	rituximab (mean 2.4 years, 5.2 treatments) vs. second line TNF-α blocker treatment	rituximab (1 course; 3 yrs treatment) vs. palliative treatment	RTX+MTX; ABA+MTX; ETA+MTX; ADA+MTX; INF+MTX	rituximab vs. an alternative TNF-alfa inhibiting treatment as second-line biological treatment after etanercept therapy	Sequences starting with one of the following biologicals: adalimumab, etanercept, infliximab, rituximab, abatacept; and synthetic DMARDs	rituximab+MTX compared to baseline

Data	Kielhorn et al., UK (2008)[52]	Vera-Llonch et al., US (2008)[121]	Lindgren et al., Sweden (2009)[66]	Brodszky et al., Hungary (2010)[23]	Hallinen et al., Finland (2010)[42]	Merkesdal et al., Germany (2010)[76]	Malottki et al., UK (2011)[70]	Benucci et al., Italy (2011)[14]
Model structure	Markov model, lifetime horizon, 6-months cycles, 10 000 simulations	patient-level simulation model, 10 years and lifetime horizon	patient-level discrete event simulation model, lifetime horizon	Markov model, lifetime horizon	Markov model, lifetime horizon, response according to ACR20, ACR50 and ACR70 determined.	Markov model, lifetime microstimulation. Response according to ACR determined and associated HAQ score	individual sampling (Birmingham RA Model – BRAM)	NA (real life experiment), 1-year horizon
Patient inputs	81% female, baseline age 52.2 yrs, body weight 78 kg, HAQ 1.88; inadequate response to two nbDMARDs and one TNFα inhibitor	women, aged 55–64 years, (HAQ 1,8, EQ-5D 0,39) with moderately to severely active RA with at least 1 TNF-α blocker failure	base case: 52-year-old female patient with a HAQ of 1.9 at the start of the second biologic and a disease duration of 12 years	predominantly women (81%), mean age 52.5 years, moderate to severe RA, failure of nbDMARDS and at least 1 TNFα inhibitor (REFLEX trial)	Identical, hypothetical RA patients cohort with 3000 patients	Individual sampling model using baseline patient characteristics from the REFLEX trial. Patients having failed at least one prior DMARD therapy and one subsequent TNF-inhibiting therapy	from registry	moderate or severe RA (DAS28 5.84 ±0.8; DAS28-CRP 5.05 ±0.9; HAQ 2.04 ±0.44) with min. 1 TNF-α blocker failure
Sources of effectiveness evidence	REFLEX trial	ATTAIN trial	rituximab: REFLEX trial; second line TNF-α data from a registry	REFLEX trial	Effectiveness from published clinical trials	adjusted RCT data, expert opinion	randomized controlled trials	real life data (n=32)

Data	Kielhorn et al., UK (2008)[52]	Vera-Llonch et al., US (2008)[121]	Lindgren et al., Sweden (2009)[66]	Brodszky et al., Hungary (2010)[23]	Hallinen et al., Finland (2010)[42]	Merkesdal et al., Germany (2010)[76]	Malottki et al., UK (2011)[70]	Benucci et al., Italy (2011)[14]
Sources of cost data	drug, administration and monitoring costs, direct medical costs (official prices)	only direct medical costs were considered, varying by HAQ	drug costs: official price lists; data of a survey were used to calculate other costs as a function of HAQ and DAS28	official price lists (infliximab dose escalation was considered)	Resource use and costs were obtained from the Finnish treatment practice, one published study, the Finnish Unit Cost list and Finnish Medicine Tariffs	drug costs: German drug retail prices for pharmacists. The HAQ score groups and related inpatient costs: German registry. Indirect costs were estimated by impaired work capacity due to RA	only direct costs; official price lists	direct medical costs
Utilities	derived from HAQ: QoL =0.76–0.28xHAQ+0.05 xfemale	EQ-5D derived from HAQ (national RA registry)	registry data were used to link utilities to HAQ and DAS28	EQ-5D derived from HAQ (linera regression)	QoL were estimated on the basis of the formula provided by Bansback et al. on the basis of HUI-3 and HAQ. ACR response	ACR response categories were converted into HAQ score improvement according to the data of the REFLEX trial	EQ-5D derived from HAQ	derived from HAQ
Discount rate	3.5%	3.0%	3.0%	5.0%	3%	3,5%	3.5%	not applied

Data	Kielhorn et al., UK (2008)[52]	Vera-Llonch et al., US (2008)[121]	Lindgren et al., Sweden (2009)[66]	Brodszky et al., Hungary (2010)[23]	Hallinen et al., Finland (2010)[42]	Merkesdal et al., Germany (2010)[76]	Malottki et al., UK (2011)[70]	Benucci et al., Italy (2011)[14]
Base case results	Scenario A, ICER: £14 690/QALY Scenario B, ICER: £11 601/QALY	ICER 10 years: $50,576/QALY, lifetime $45,979.	rituximab is dominant (incremental cost: - €2500, incremental QALY: 0.2)	1 course RTX, ICER: –€31,140/QALY, 3-year RTX: €26,223/QALY from societal perspective.	The ICERs of RTX compared to BSC was €30248/QALY; ADA vs. €50 941/QALY, ETA vs BSC €50 372/QALY, INF vs. BSC €36121/QALY, ABA vs. BSC €67 003/QALY.	ICER RTC vs stand seq. €24,517/QALY. When indirect costs were also included, the ICER was €15,565.	Compared to conventional DMARD alone RTX dominates TNF inhibitors (e.g. RTX-sDMARD: £21,100/QALY; ADA-RTX dominant, ETA-RTX dominant, INF-RTX dominant)	€23,696/QALY
Key sensitivity analysis	RTX dosing frequency: 12 months: 9759/QALY; 6 months: 23 774/QALY	ICER 10 years: $46,675 - $80,673/QALY; lifetime: 40,836 - 59,875/QALY.	Only if rituximab were administered every 4 months or less are costs for this strategy higher	ICERs -€31,140€/QALY and €21,980/QALY, respectively from the health care payer perspective (RTX vs. switch to a 2nd biological: RTX dominant)	Results were sensitive to the length of the treatment, negative QALYs, the discount rate and the impact of the Finnish system	Results were sensitive to the RTX dosing scheme, on changes to HAQ deterioration, discounting, rebound effect value, the model entry age or entry HAQ score, the risk multiplier and the effect of work capacity	the assumed time between RTX treatment had significant effect	subgroup analysis by the number of TNF- α blocker failures: ICER is more beneficial in patients with only 1 TNF-α blocker failure: €14,447/QALY

Table 9 DMARD naive RA patients - Quality assessment of the health economic evaluations by the Drummond checklist

✔ or X or NA (not applicable)

Checklist	Davies et al., US (2009)[30]	Kobelt et al., Sweden (2009)[57]	Van den Hout et al., The Netherlands (2009)[116]	Schipper et al., The Netherlands (2011)[98]
Research question				
1. Costs and effects examined □	✔	✔	✔	✔
2. Alternatives compared ×	✔	✔	✔	✔
3. The viewpoint(s)/perspective of the analysis is clearly stated(e.g. NHS, society)	✔	✔	✔	✔
Selection of alternatives				
4. All relevant alternatives are compared (including 'do nothing' if applicable)	✔	✔	✔	✔
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✔	✔	✔	✔
6. The rationale for choosing the alternative programmes or interventions compared is stated	✔	✔	✔	✔
Form of evaluation				
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✔	✔	✔	✔
8. If a cost-minimisation design is chosen, have equivalentoutcomes been adequately demonstrated?	NA	NA	NA	NA
Effectiveness data				

Checklist	Davies et al., US (2009)[30]	Kobelt et al., Sweden (2009)[57]	Van den Hout et al., The Netherlands (2009)[116]	Schipper et al., The Netherlands (2011)[98]
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✔	✔	✔	✔
10. Effectiveness data from RCT or review of RCTs	✔	✔	✔	X (cohort, registry)
11. Potential biases identified (especially if data not from RCTs)	X	X	✔	✔
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✔	✔	✔	NA
Costs				
13. All of the important and relevant resource use included	✔	✔	X	✔
14. All of the important and relevant resource use measured accurately (with methodology)	✔	✔	X	✔
15. Appropriate unit costs estimated (with methodology)	✔	X	✔	✔
16. Unit costs reported separately from resource use data	X	NA	X	✔
17. Productivity costs treated separately from other costs	✔	X	✔	✔
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	X	✔	✔	✔
Benefit measurement and valuation				
19. The primary outcome measure(s) for the economic evaluation	✔	✔	✔	✔
20. Methods to value health states and other benefits are stated	✔	✔	✔	✔

Checklist	Davies et al., US (2009)[30]	Kobelt et al., Sweden (2009)[57]	Van den Hout et al., The Netherlands (2009)[116]	Schipper et al., The Netherlands (2011)[98]
21. Details of the individuals from whom valuations were obtained are given	✔	✔	✔	✔
Decision modelling				
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✔	✔	✔	✔
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✔	✔	X	✔
24. All model outputs described adequately	✔	✔	✔	✔
Discounting				
25. Discount rate used for both costs and benefits	✔	✔	✔	✔
26. Do discount rates accord with NHS guidance?	X	X	X	✔(The Netherlands)
Allowance for uncertainty				
Stochastic analysis of patient-level data				
27. Details of statistical tests and CIs are given for stochastic data	✔	X	✔	✔
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	✔	✔	✔	✔
29. Sensitivity analysis used to assess uncertainty in nonstochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✔	✔	X	✔

Table 10 RA patients who failed at least one synthetic DMARD - Quality assessment of the health economic evaluations by the Drummond checklist

✔ or X or NA (not applicable)

Checklist	Vera-Llonch et al., US (2008)[121]	Virkki et al., Finland (2008)[122]	Kobelt et al., Sweden (2009)[58]	Sany et al., France (2009)[95]	Lekander et al., Sweden (2010)[64]	Scultze-Koops et al., Germany (2009)[100]	Soini et al., Finland (2012)[106]	Diamantopoulos et al, Italy (2012)[32]
Research question								
1. Costs and effects examined □	✔	✔	✔	✔	✔	✔	✔	✔
2. Alternatives compared ×	✔	✔	✔	✔	✔	✔	✔	✔
3. The viewpoint(s)/perspective of the analysis is clearly stated(e.g. NHS, society)	✔	✔	✔	✔	✔	✔	✔	✔
Selection of alternatives								
4. All relevant alternatives are compared (including 'do nothing' if applicable)	X (no other biologic therapies were considered)	X (no other biological drugs were considered)	✔	X (health status and costs before and after infliximab treatment; no other alternatives)	✔	✔	X (infliximab was considered only as second line biologic therapy)	X (certolizumab pegol and golimumab not included)
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✔	✔	✔	✔	X	✔	✔	✔
6. The rationale for choosing the alternative programmes or interventions compared is stated	✔	X	✔	✔	✔	✔	✔	✔
Form of evaluation								

Checklist	Vera-Llonch et al., US (2008)[121]	Virkki et al., Finland (2008)[122]	Kobelt et al., Sweden (2009)[58]	Sany et al., France (2009)[95]	Lekander et al., Sweden (2010)[64]	Scultze-Koops et al., Germany (2009)[100]	Soini et al., Finland (2012)[106]	Diamantopoulos et al, Italy (2012)[32]
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✔	✔	✔	✔	✔	✔	✔	✔
8. If a cost-minimisation design is chosen, have equivalentoutcomes been adequately demonstrated?	NA	NA	NA	NA	NA	NA	NA	NA
Effectiveness data								
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✔	✔	✔	✔	✔	✔	✔	✔
10. Effectiveness data from RCT or review of RCTs	✔	X	X (registry)	X (registry)	X	X	✔	✔
11. Potential biases identified (especially if data not from RCTs)	✔	X	X	X	X	X	✔	✔
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✔	X	X	X	X	X	✔	✔
Costs								
13. All of the important and relevant resource use included	X (only medical treatment costs)	X (only direct costs)	✔	✔	✔	✔	✔(indirect costs in the sens. analysis)	X (only direct costs)
14. All of the important and relevant resource use measured accurately (with methodology)	✔	✔	✔	✔	✔	X	✔	✔
15. Appropriate unit costs estimated (with methodology)	✔	✔	✔	✔	X	X	✔	✔

Checklist	Vera-Llonch et al., US (2008)[121]	Virkki et al., Finland (2008)[122]	Kobelt et al., Sweden (2009)[58]	Sany et al., France (2009)[95]	Lekander et al., Sweden (2010)[64]	Scultze-Koops et al., Germany (2009)[100]	Soini et al., Finland (2012)[106]	Diamantopoulos et al, Italy (2012)[32]
16. Unit costs reported separately from resource use data	✔	✔	✔	✔	NA	NA	✔	✔
17. Productivity costs treated separately from other costs	NA (no indirect costs)	NA (no indirect costs)	✔	✔	X	✔	✔	NA (no indirect costs)
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	✔	✔	✔	✔	✔	✔	✔	✔
Benefit measurement and valuation								
19. The primary outcome measure(s) for the economic evaluation	✔	✔	✔	✔	✔	✔	✔	✔
20. Methods to value health states and other benefits are stated	✔	✔	✔	✔	✔	✔	✔	✔
21. Details of the individuals from whom valuations were obtained are given	✔	✔	✔	✔	✔	✔	✔	✔
Decision modelling								
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✔	NA (follow up data)	✔	NA (registry data)	✔	✔	✔	✔
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✔	NA	✔	NA	X	✔	✔	✔
24. All model outputs described adequately	✔	NA	✔	NA	✔	✔	✔	✔
Discounting								
25. Discount rate used for both costs and benefits	✔	X	✔	X	✔	✔	✔	✔

Checklist	Vera-Llonch et al., US (2008)[121]	Virkki et al., Finland (2008)[122]	Kobelt et al., Sweden (2009)[58]	Sany et al., France (2009)[95]	Lekander et al., Sweden (2010)[64]	Scultze-Koops et al., Germany (2009)[100]	Soini et al., Finland (2012)[106]	Diamantopoulos et al, Italy (2012)[32]
26. Do discount rates accord with NHS guidance?	✔ (US)	NA	✔	NA	X	X	✔(Finland)	✔ (Italy)
Allowance for uncertainty								
Stochastic analysis of patient-level data								
27. Details of statistical tests and CIs are given for stochastic data	✔	X	✔	X	X	X	✔	✔
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	✔	X	✔	X	X	✔	✔	✔
29. Sensitivity analysis used to assess uncertainty in nonstochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✔	X	✔	X	✔	✔	✔	✔

Table 11 RA patients who failed at least one biologic DMARD - Quality assessment of the health economic evaluations by the Drummond checklist

✔ or X or NA (not applicable)

Checklist	Kielhorn et al., UK (2008)[52]	Vera-Llonch et al., US (2008)[121]	Lindgren et al., Sweden (2009)[66]	Brodszky et al., Hungary (2010)[23]	Hallinen et al., Finland (2010)[42]	Merkesdal et al., Germany (2010)[76]	Malottki et al., UK (2011)[70]	Benucci et al., Italy (2011)[14]
Research question								
1. Costs and effects examined □	✔	✔	✔	✔	✔	✔	✔	✔
2. Alternatives compared ×	✔	✔	✔	✔	✔	✔	✔	✔
3. The viewpoint(s)/perspective of the analysis is clearly stated(e.g. NHS, society)	✔	✔	✔	✔	✔	✔	✔	X
Selection of alternatives								
4. All relevant alternatives are compared (including 'do nothing' if applicable)	✔	X (switch between TNF inhibitors ignored)	✔	✔	✔	✔	✔	X (compared to baseline data)
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✔	✔	✔	✔	✔	✔	✔	✔
6. The rationale for choosing the alternative programmes or interventions compared is stated	✔	✔	✔	✔	✔	✔	✔	✔
Form of evaluation								
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✔	✔	✔	✔	✔	✔	✔	✔
8. If a cost-minimisation design is chosen, have equivalentoutcomes	NA	NA	NA	✔(sensitivity	NA	NA	NA	NA

Checklist	Kielhorn et al., UK (2008)[52]	Vera-Llonch et al., US (2008)[121]	Lindgren et al., Sweden (2009)[66]	Brodszky et al., Hungary (2010)[23]	Hallinen et al., Finland (2010)[42]	Merkesdal et al., Germany (2010)[76]	Malottki et al., UK (2011)[70]	Benucci et al., Italy (2011)[14]
been adequately demonstrated?				analysis)				
Effectiveness data								
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✔	✔	✔	✔	✔	✔	✔	✔
10. Effectiveness data from RCT or review of RCTs	✔	✔	✔	✔	✔	✔	✔	X (real life data)
11. Potential biases identified (especially if data not from RCTs)	✔	✔	✔	✔	X	X	✔	X
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✔	NA	NA	✔	✔	✔	✔	NA
Costs								
13. All of the important and relevant resource use included	X (only direct medical costs)	X (only direct medical costs)	✔	✔	✔	✔	X (only direct costs)	X (only direct medical costs)
14. All of the important and relevant resource use measured accurately (with methodology)	✔	✔	✔	✔	✔	✔	✔	✔
15. Appropriate unit costs estimated (with methodology)	✔	✔	✔	✔	✔	X	✔	✔
16. Unit costs reported separately from resource use data	✔	✔	✔	✔	✔	NA	✔	X
17. Productivity costs treated separately from other costs	NA (no indirect costs)	NA (no indirect costs)	✔	✔	X	✔	NA (only direct costs)	NA (no indirect costs)

Checklist	Kielhorn et al., UK (2008)[52]	Vera-Llonch et al., US (2008)[121]	Lindgren et al., Sweden (2009)[66]	Brodszky et al., Hungary (2010)[23]	Hallinen et al., Finland (2010)[42]	Merkesdal et al., Germany (2010)[76]	Malottki et al., UK (2011)[70]	Benucci et al., Italy (2011)[14]
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	✔	✔	✔	✔	✔	✔	✔	X
Benefit measurement and valuation								
19. The primary outcome measure(s) for the economic evaluation	✔	✔	✔	✔	✔	✔	✔	✔
20. Methods to value health states and other benefits are stated	✔	✔		✔	✔	✔	✔	✔
21. Details of the individuals from whom valuations were obtained are given	✔	✔	✔	✔	✔	✔	✔	✔
Decision modelling								
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✔	✔	✔	✔	✔	✔	✔	NA
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✔	✔	✔	X (partly)	✔	✔	✔	NA
24. All model outputs described adequately	✔	✔	✔	✔	✔	✔	✔	NA
Discounting								
25. Discount rate used for both costs and benefits	✔	✔	✔	✔	✔	✔	✔	X
26. Do discount rates accord with NHS guidance?	✔	✔ (US)	✔ (Sweden)	✔(HUN)	X	X	✔	X
Allowance for uncertainty								
Stochastic analysis of patient-level data								

Checklist	Kielhorn et al., UK (2008)[52]	Vera-Llonch et al., US (2008)[121]	Lindgren et al., Sweden (2009)[66]	Brodszky et al., Hungary (2010)[23]	Hallinen et al., Finland (2010)[42]	Merkesdal et al., Germany (2010)[76]	Malottki et al., UK (2011)[70]	Benucci et al., Italy (2011)[14]
27. Details of statistical tests and CIs are given for stochastic data	X	✔	✔	X	X	✔	✔	X
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	X	✔	✔	X	✔	✔	✔	X
29. Sensitivity analysis used to assess uncertainty in nonstochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✔	✔	✔	X (partly)	✔	✔	✔	X

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8 Appendices

8.1 Search terms for RCTs and meta-analyses

"arthritis, rheumatoid"[MeSH Terms] AND (abatacept OR adalimumab OR certolizumab OR golimumab OR etanercept OR infliximab OR rituximab OR tocilizumab) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[MeSH Terms:noexp] OR randomly[tiab] OR trial[ti]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND ("2009/11/01"[PDAT] : "2012/03/31"[PDAT])

8.2 Search results and study selection

See file: ***infliximab.ra.hta.appendix.5.2.literaturesearch.docx***

8.3 Quality assessment of included studies; detailed description of Jadad score

Calculating Jadad score is based on a three-point questionnaire published by Jadad et al.[46]. Each question can be answered with either a yes or a no. Each yes scores one point, each no zero points. The questions were:

1. Was the study described as randomized?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

To receive the corresponding point, an article should describe the number of withdrawals and dropouts, in each of the study groups, and the underlying reasons.

Additional points were given if:

The method of randomisation was described in the paper, and that method was appropriate.

The method of blinding was described, and it was appropriate.

Points would however be deducted if:

The method of randomisation was described, but was inappropriate.

The method of blinding was described, but was inappropriate.

A paper reporting a clinical trial could therefore receive a Jadad score of between zero and five.

8.4 Description of mixed treatment models and WinBUGS codes

All MTC models used the odds ratio as the measure of relative treatment effect and assumed that treatment effects on the odds-ratio scale were multiplicative and exchangeable between trials. Each model was run with 3 chains and 10,000 burn-in iterations in order to limit the influence of the initial values on the simulated posterior distribution. A further 20,000 MCMC iterations were run, and the sampled values were used to estimate posterior means and 95% credibility intervals (CrIs). Credibility intervals are the Bayesian equivalent of classical confidence intervals.

Convergence was assessed based on Brooks-Gelman-Rubin (BGR) plot. The accuracy of the posterior estimates was done by calculating the Monte Carlo error for each parameter. As a rule of thumb, the Monte Carlo error for each parameter of interest is less than about 5% of the sample standard deviation. The overall residual deviance was compared to the number of independent data points to check if the model fit the data satisfactory. For a Binomial likelihood, each trial arm contributes 1 independent data point.

Differences between treatments were considered significantly significant at the 0.05 level if the 95% CrIs around the odds ratio did not cross 1.

WinBUGS code for mixed treatment comparison

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         # LOOP THROUGH STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control
arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)            # vague priors for all trial
baselines
    for (k in 1:na[i]) {              # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
        logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
        rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
            +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))          }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {              # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])            # Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt)[  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k]  <-  exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
}
}
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- nt+1-rank(d[],k) # assumes events are "good"
#rk[k] <- rank(d[],k) # assumes events are "bad"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
}

}                              # *** PROGRAM ENDS
```

8.5 Detailed description of RCTs included

Table 12 Bathon 2000, etanercept

Examination	multicenter, randomized, placebo controlled study
Number of patients	632
Inclusion criteria	- at least 18 years of age - had rheumatoid arthritis for no more than three years - had no other important concurrent illnesses, and had not been treated with methotrexate Stable doses of nonsteroidal antiinflammatory drugs and prednisone («10 mg daily) were allowed.
Exclusion criteria	- got disease-modifying antirheumatic drugs (including hydroxychloroquine and sulfasalazine) less than four weeks before the study began
Therapy	- 10 mg etanercept twice-weekly + 3 placebo tablets weekly - 25 mg etanercept twice-weekly + 3 placebo tablets weekly - three (2.5-mg) tablets of methotrexate weekly and twice weekly subcutaneous injections
Rescue therapy (number of patients)	0
Follow-up time	12 months
Primary endpoint	ACR-N (20, 50, 70) and change in total Sharp core
Secondary endpoints	
JADAD score	1
Comment	

Table 13 Breedveld 2006, adalimumab

Examination	multicenter, double-blind, phase III, active comparator-controlled study
Number of patients	799
Inclusion criteria	- active disease of <3 years' duration - had never been treated with MTX - patients have to be 18 years of age or older and have to have disease that fulfilled the American College of Rheumatology 1987 revised criteria for the classification of RA with a disease duration of 3 years. - patients had to have had 8 swollen joints, 10 tender joints, and an erythrocyte sedimentation rate of 28mm/hour or C-reactive protein (CRP) concentration of 1.5 mg/dl, and had to either be rheumatoid factor positive or have had at least 1 joint erosion
Exclusion criteria	- patients who had received treatment with MTX, cyclophosphamide, cyclosporine, azathioprine, or 2 other DMARDs, were excluded
Therapy	- adalimumab 40 mg subcutaneously every other week plus oral MTX - adalimumab 40 mg subcutaneously every other week, - weekly oral MTX
Rescue therapy (number of paients)	0
Follow-up time	52 weeks
Primary endpoint	ACR50 and change in total Sharp score
Secondary endpoints	DAS28, HAQ-DI, change from baseline the modified total Sharp

	score at year 2, ACR20, ACR50, ACR70, ACR90 at year 2
JADAD score	5
Comment	

Table 14 Clair 2004, infliximab

Examination	randomized, placebo controlled study
Number of patients	1049
Inclusion criteria	- at least 18 years old but no older than 75 years - met the 1987 revised criteria of the ACR (formerly, the American Rheumatism Association) for the classification of RA - had persistent synovitis for 3 months and 3 years, 10 swollen joints, 12 tender joints - patients had to have had one or more of the following: a positive test result for serum rheumatoid factor, radiographic erosions of the hands or feet, or a serum C-reactive protein (CRP) level 2.0 mg/dl
Exclusion criteria	- had any prior treatment with MTX, had received other DMARDs within 4 weeks of entry (or leflunomide within the past 6 months), or had been treated with infliximab, etanercept, adalimumab, or other anti-TNFagent - infection with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus as well as a history of active or past tuberculosis, congestive heart failure, or lymphoma or other malignancy within the past 5 years (excluding excised skin cancers)
Therapy	- Infliximab 3mg/kg + methotrexate - Infliximab 6mg/kg + methotrexate - placebo + methotrexate
Rescue therapy (number of patients)	0
Follow-up time	54 weeks
Primary endpoint	ACR-N, and change in total Sharp score, HAQ*
Secondary endpoint	
JADAD score	3
Comment	* The primary end point for improvement in physical function was the change from baseline in HAQ scores averaged over weeks 30–54

Table 15 Cohen 2006, rituximab

Examination	multicenter, randomized, double-blind, placebo-controlled, phase III trial
Number of patients	520
Inclusion criteria	- patients had RA for at least 6 months, according to the ACR 1987 revised criteria and had active disease, which was defined as 8 swollen joints and 8 tender joints, a C-reactive protein (CRP) level 1.5 mg/dl or an erythrocyte sedimentation rate (ESR) 28 mm/hour, and radiographic evidence of at least 1 joint with a definite erosion attributable to RA, as determined by a central reading site - patients had to be taking MTX (10–25 mg/week) for at least 12 weeks prior to screening, with the last 4 weeks at a stable dosage
Exclusion criteria	- a history of a rheumatic autoimmune disease other than RA (except secondary Sjögren's syndrome), significant systemic involvement secondary to RA (vasculitis, pulmonary fibrosis, or Felty's syndrome), or ACR functional class IV disease
Therapy	- rituximab 2x500mg + MTX - placebo + MTX
Rescue therapy (number of patients)	81
Follow-up time	24 weeks
Primary endpoint	ACR20
Secondary endpoints	ACR50, ACR70, DAS28, EULAR criteria and the individual parameters of the ACR improvement criteria: swollen joint count, tender joint count, patient's and physician's global assessments of disease activity, patient's assessment of pain, patient's assessment of disability the CRP level, and the ESR
JADAD score	5
Comment	

Table 16 Edwards 2004, rituximab

Examination	multicenter, randomized, double-blind, controlled study
Number of patients	161
Inclusion criteria	- at least 21 years of age, fulfilled the revised 1987 American Rheumatism Association criteria, and had active disease despite treatment with at least 10 mg of methotrexate per week - active disease was defined by the presence of at least eight swollen and eight tender joints and at least two of the following: a serum C-reactive protein level of at least 15 mg per liter, an erythrocyte sedimentation rate of at least 28 mm per hour, or morning stiffness lasting longer than 45 minutes - patients were seropositive for rheumatoid factor, as defined by a plasma rheumatoid factor level of at least 20 IU per milliliter
Exclusion criteria	- had an autoimmune disease other than rheumatoid arthritis (except concurrent Sjogren's syndrome), American Rheumatism Association functional class IV disease, active rheumatoid vasculitis, a history of systemic diseases associated with arthritis, chronic fatigue syndrome, serious and uncontrolled coexisting diseases, active infection, a history of recurrent clinically significant infection or of recurrent bacterial infections with encapsulated organisms, primary or secondary immunodeficiency, or a history of cancer
Therapy	- Rituximab 2x500mg

	- Rituximab 2x500mg +cyclophosphamide - Rituximab 2x500mg + MTX - Placebo + MTX
Rescue therapy (number of patients)	0
Follow-up time	24 weeks
Primary endpoint	ACR50
Secondary endpoints	ACR20, ACR70, a change in the disease-activity score, EULAR response
JADAD score	3
Comment	

Table 17 Emery 2008, etanercept

Examination	double-blind, randomised, parallel-group, multicentre, outpatient study with two periods
Number of patients	542
Inclusion criteria	- age 18 years or older with diagnosis of adult-onset rheumatoid arthritis - disease duration of at least 3 months but not more than 2 years - DAS28 of 32 or more, and either Westergren ESR of 28 mm/h or more or C-reactive protein of 20 mg/L or more
Exclusion criteria	- had received previous treatment with methotrexate, etanercept, or another TNF antagonist at any time or had received treatment with other DMARDs or corticosteroid injections in the 4 weeks before baseline visits - important concurrent medical disease
Therapy	- Etanercept 50 mg weekly + MTX - Placebo + MTX
Rescue therapy (number of patients)	0
Follow-up time	52 weeks
Primary endpoint	DAS28, and change in total Sharp score
Secondary endpoints	health assessment questionnaire disability index and stopping work were analysed as change from baseline by use of ANCOVA
JADAD score	5
Comment	comparison with other randomised clinical trials of early rheumatoid arthritis

Table 18 Emery 2008, tocilizumab

Examination	phase III, randomised, double-blind, placebo controlled, parallel group study
Number of patients	499
Inclusion criteria	- 18 years of age and older with moderate to severe active RA and failure to respond or intolerance to one or more TNF antagonists within the past year - had active RA for 6 months or more, swollen joint count (SJC) of 6 or more, tender joint count (TJC) of 8 or more, and C-reactive protein (CRP) greater than 1.0 mg/dl or erythrocyte sedimentation rate (ESR) greater than 28 mm/h at baseline - discontinued etanercept (>2 weeks), infliximab or adalimumab (>8 weeks), leflunomide (>12 weeks) and all DMARD other than methotrexate before receiving study medication

	- had to be treated with methotrexate for 12 weeks or more before baseline (stable dose >8 weeks)
Exclusion criteria	- treatment with celldepleting agents, uncontrolled medical conditions history of other inflammatory diseases or functional class 4 RA, history of malignancies or recurrent infections, primary or secondary immunodeficiency, haemoglobin less than 8.5 g/dl, leucopenia, neutropenia, thrombocytopenia, abnormal liver function, triglycerides greater than 10 mmol/l, or recognised active tuberculosis, hepatitis B, or hepatitis C
Therapy	- Tocilizumab 8mg/kg + MTX - Tocilizumab 4mg/kg + MTX - Placebo + MTX
Rescue therapy (number of patients)	117 patients
Follow-up time	24 weeks
Primary endpoint	ACR20
Secondary endpoints	efficacy measures: adverse events, infections, infusion reactions
JADAD score	3
Comment	

Table 19 Emery 2009, golimumab

Examination	phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study followed by an open-label 5-year extension
Number of patients	637
Inclusion criteria	- adults who had RA, according to the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria, for at least 3 months before administration of the initial study agent and had not received more than 3 weekly doses of oral MTX as treatment of RA - had active RA, with at least 4 swollen joints and at least 4 tender joints at both screening and baseline, and met at least 2 of the following criteria at screening and/or baseline: 1) C-reactive protein (CRP) level of _1.5 mg/dl or erythrocyte sedimentation rate (ESR) of 28 mm/hour according to the Westergren method, 2) morning stiffness lasting 30 minutes or longer, 3) bone erosion by radiography and/or magnetic resonance imaging prior to initiation of treatment with the study agent, or 4) anti–cyclic citrullinated peptide antibody positivity or rheumatoid factor positivity
Exclusion criteria	- had previously received infliximab, etanercept, adalimumab, rituximab, natalizumab, or cytotoxic agents, including chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents
Therapy	- Golimumab 100 mg + MTX - Golimumab 50 mg + MTX - Golimumab 100 mg + placebo - Placebo + MTX
Rescue therapy (number of patients)	0
Follow-up time	52 weeks
Primary endpoint	ACR-50 at week 24, and change in total Sharp score at week 52
Secondary endpoint	
JADAD score	5

Comment	The primary end point was the difference in the ACR50 response at week 24 between groups 3 and 4 combined (combined group) versus group 1 and a pairwise comparison (group 3 or group 4 versus group 1). ACR20, ACR70, and ACR90 responses were also measured.

Table 20 Emery 2010, rituximab

Examination	multicentre, randomized, double-blind, placebo-controlled, phase III study
Number of patients	512
Inclusion criteria	- aged 18–80 years with RA according to American College of Rheumatology (ACR) criteria for ≥6 months, which was active despite MTX (10−25 mg/week for at least 12 weeks) - active disease was defined as swollen joint count (SJC) and tender joint count (TJC) both ≥8, and either C reactive protein (CRP) ≥0.6 mg/dl or erythrocyte sedimentation rate (ESR) ≥28 mm/h - had to have an absolute neutrophil count ≥1500 cells/µl, a haemoglobin level ≥8 g/dl and IgM and IgG levels of ≥40 and ≥500 mg/dl, respectively
Exclusion criteria	- had not previously received biological treatment for RA
Therapy	- Rituximab 2x1000 mg + MTX - Rituximab 2x500 mg + MTX - Placebo + MTX
Rescue therapy (number of patients)	26
Follow-up time	48 weeks
Primary endpoint	ACR20
Secondary endpoints	ACR50, ACR70, EULAR, DAS28-ESR and remission, HAQ-DI, MCIDs, FACIT-F
JADAD score	3
Comment	

Table 21 Emery 2006, rituximab

Examination	phase IIb, randomized, doubleblind, double-dummy, placebo-controlled, international multifactorial trial
Number of patients	465
Inclusion criteria	- between 18 and 80 years of age and had presented at least 6 months prior to randomization with moderate or severe RA (diagnosed according to the American College of Rheumatology despite ongoing treatment with MTX at a dosage of 10–25 mg/week (orally or parenterally) for at least 12 weeks before randomization, with a stable dosage during the last 4 weeks - active disease was defined as a swollen and tender joint count 8 and either an erythrocyte sedimentation rate 28 mm/hour or a C-reactive protein (CRP) serum level 1.5 mg/dl - must have failed prior treatment, manifesting as a lack or loss of response to treatment with at least 1 but not more than 5 DMARDs (other than MTX) and/or biologic response modifiers - discontinued DMARDs (except MTX) and biologic therapy at least 4 weeks before randomization and discontinued infliximab, adalimumab, or leflunomide at least 8 weeks before randomization
Exclusion criteria	- concomitant treatment with any DMARD (other than MTX), anti–tumor necrosis factor, or other biologic therapy

	- had significant systemic involvement secondary to RA, evidence of significant other illnesses or laboratory abnormalities, a history of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies, or previous treatment with rituximab or any lymphocyte-depleting therapies - had a history of recurrent significant infection
Therapy	- Rituximab 2x1000 mg + (10-25mg) MTX weekly - Rituximab 2x500 mg + (10-25mg) MTX weekly - Placebo + (10-25mg) MTX weekly
Rescue therapy (number of patients)	
Follow-up time	24 weeks
Primary endpoint	ACR20
Secondary endpoints	ACR50, ACR70 and the effect on individual parameters of the ACR improvement criteria, DAS28, EULAR, FACIT-F subscore, HAQ-DI
JADAD score	5
Comment	Rituximab was administered by intravenous (IV) infusion in RF-positive patients: placebo, 500 mg or 1,000 mg on days 1 and 15 (total dose 0 mg, 1,000 mg, and 2,000 mg). Glucocorticoids were administered as placebo methylprednisolone, given IV 30–60 minutes before the infusion of rituximab (or rituximab placebo) on days 1 and 15, premedication methylprednisolone 100 mg, given IV on days 1 and 15 (250 mg prednisone equivalent), or premedication methylprednisolone 100 mg, given IV on days 1 and 15 plus 60 mg of oral prednisone on days 2–7 and 30 mg on days 8–14 (total glucocorticoid dose 820 mg prednisone equivalent). RF-negative patients received either placebo or rituximab (2 1,000-mg infusions), with or without glucocorticoids. All patients received a weekly regimen of MTX (10–25 mg orally or parenterally) with folate (_5 mg/week).

Table 22 Fleischmann 2009, certolizumab

Examination	multicentre, randomised, double-blind, placebo-controlled study
Number of patients	220
Inclusion criteria	- aged 18–75 years, had adult onset RA, defined by the 1987 American College of Rheumatology (ACR) criteria of duration >6 months, and had failed >1 prior DMARD due to lack of efficacy or intolerance - had to have active disease at screening and baseline, defined by >9 (out of 68) tender joints and >9 (out of 66) swollen joints and >1 of the following: >45 min of morning stiffness, erythrocyte sedimentation rate (ESR; Westergren method) >28 mm/h,or C-reactive protein (CRP)10 mg/litre
Exclusion criteria	- had any inflammatory arthritis other than RA or a history of chronic, serious or life-threatening infection, any current infection, a history of or a chest x ray suggesting tuberculosis or a positive (defined by local practice) purified protein derivative (PPD) skin test - had received biological therapies for RA within 6 months, or prior treatment with TNFa inhibitors
Therapy	- Certolizumab pegol 400mg every 4 weeks - Placebo every 4 weeks
Rescue therapy (number of patients)	

Follow-up time	24 weeks
Primary endpoint	ACR20
Secondary endpoint	ACR50, ACR70, ACR component scores, DAS28 (ESR3), patient-reported outcomes, safety, HAQ-DI, HrQOL, VAS, mBPI, FAS
JADAD score	5
Comment	

Table 23 Furst 2003, adalimumab

Examination	double-blind, randomized, controlled trial
Number of patients	636
Inclusion criteria	- 18 years of age or older - had active RA at both screening and baseline visits defined by at least 6 swollen joints and at least 9 tender joints (excluding distal interphalangeal joints), and met the 1987 revised American College of Rheumatology (ACR) criteria9 for diagnosis of RA for at least 3 months
Exclusion criteria	- used other biologic DMARD in RA - treated with anti-CD4 therapy or biologic DMARD (e.g., TNF antagonists, interleukin-1 receptor antagonists) and/or with a history of an active inflammatory arthritide other than RA, a history of active listeriosis or mycobacterial infection, a major episode of infection (i.e., infections requiring hospitalization, treatment with intravenous antibiotics within 30 days prior to screening, or oral antibiotics within 14 days prior to screening), and any uncontrolled medical condition - a variety of comorbid diseases
Therapy	- Adalimumab 40 mg every other week + DMARD - Placebo + DMARD
Rescue therapy (number of patients)	
Follow-up time	24 weeks
Primary endpoint	safety: adverse events, physical examination findings, and standard laboratory test results
Secondary endpoints	Efficacy was the secondary endpoint of this study and was assessed as ACR20, ACR50, and ACR70 responses
JADAD score	3
Comment	

Table 24 Genovese 2005, abatacept

Examination	randomized, double-blind, phase 3 trial
Number of patients	393
Inclusion criteria	- met the American College of Rheumatology (ACR) criteria for rheumatoid arthritis, were at least 18 years of age, had had rheumatoid arthritis for at least one year, and had an inadequate response to anti TNF*a* therapy with etanercept, infliximab, or both at the approved dose after at least three months of treatment - at randomization, patients had to have at least 10 swollen joints, at least 12 tender joints, and C-reactive protein levels of at least 1 mg per deciliter (upper limit of the normal range, 0.5) - patients had to have been taking an oral DMARD or anakinra for at least 3 months, and the dose had to have been stable for at least 28 days - all users were required to stop taking etanercept or infliximab for at least 28 or 60 days, respectively, before undergoing randomization

Exclusion criteria	
Therapy	- Abatacept 10 mg + DMARD - Placebo + DMARD
Rescue therapy (number of patients)	
Follow-up time	6 months
Primary endpoint	ACR20, HAQ-DI
Secondary endpoint	ACR50, ACR70
JADAD score	5
Comment	

Table 25 Genovese 2008, tocilizumab

Examination	phase III, randomized, double-blind, placebo-controlled
Number of patients	1220
Inclusion criteria	- at least 18 years of age with moderate-tosevere RA of 6 months' duration, diagnosed according to the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria for the classification of RA (21), with a swollen joint count (SJC) of 6, a tender joint count (TJC) of 8, and a C-reactive protein (CRP) level 1 mg/dl or an erythrocyte sedimentation rate (ESR) 28 mm/hour were enrolled - had received stable doses of permitted DMARDs (methotrexate, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide) for 8 weeks prior to study entry
Exclusion criteria	- unsuccessfully treated with an anti-TNF agent or were previously treated with any cell-depleting therapy
Therapy	- Tocilizumab 8mg/kg + DMARD every 4 weeks - Placebo + DMARD every 4 weeks
Rescue therapy (number of patients)	64
Follow-up time	24 weeks
Primary endpoint	ACR20
Secondary endpoint	ACR50, ACR70, DAS28, EULAR, ESR, HAQ, FACIT-F, systematic markers
JADAD score	5
Comment	

Table 26 Jones 2010, tocilizumab

Examination	double-blind, randomised, double-dummy, parallel-group study
Number of patients	673
Inclusion criteria	- > 18 years, with moderate to severe RA for >3 months. Active RA was defined by the presence of >6 swollen joints (SJC) from a total of 66, >8 tender joints (TJC) from a total of 68, and a C-reactive protein (CRP) level >1 mg/dl or erythrocyte sedimentation rate (ESR) >28 mm/h - wanted to become pregnant
Exclusion criteria	- had clinically unstable concurrent illnesses (and screened according to local standards and also excluded if they had active or untreated latent tuberculosis), had been unsuccessfully treated with an anti-TNFa agent, had received methotrexate in the 6 months preceding randomisation or discontinued previous methotrexate treatment because of clinically important adverse effects or lack of efficacy
Therapy	- Tocilizumab 8mg/kg every 4 weeks

	- Methotrexate (7,5-20mg/week)
Rescue therapy (number of patients)	32
Follow-up time	24 weeks
Primary endpoint	ACR20
Secondary endpoints	ACR50, ACR70, DAS28 (ESR), EULAR, HAQ-DI
JADAD score	5
Comment	

Table 27 Keystone 2009, golimumab

Examination	phase III, multicentre, randomised, double-blind, placebo controlled trial
Number of patients	444
Inclusion criteria	- 18 years of age or older, had a diagnosis of RA according to the revised 1987 criteria of the American College of Rheumatology (ACR), for at least 3 months before screening, and were to have been on a stable methotrexate dose of 15 mg/week or greater but 25 mg/week or less during the 4-week period immediately preceding screening - patients were to have tolerated 15 mg/ week or greater of methotrexate for at least 3 months before screening - required to have active RA, defined as four of more swollen joints (out of 66 total) and four or more tender joints (out of 68 total) and at least two of the following: (1) C-reactive protein (CRP) of 1.5 mg/dl or greater (normal range 0–0.6 mg/dl) or erythrocyte sedimentation rate (ESR) by the Westergren method of 28 mm/h or greater; (2) at least 30 minutes of morning stiffness; (3) bone erosion determined by x ray and/or magnetic resonance imaging; or (4) anticyclic citrullinated peptide antibody or rheumatoid factor positiv test results
Exclusion criteria	- had a known hypersensitivity to human immunoglobulin proteins or other components of golimumab - any previous use of any anti- TNF agent, rituximab, natalizumab or cytotoxic agents - should not have received anakinra; disease-modifying antirheumatic drugs other than methotrexate; or intravenous, intramuscular, or intra-articular corticosteroids within 4 weeks before the first dose of study agent or alefacept or efalizumab within 3 months before the first dose of the study agent
Therapy	- Golimumab 100mg + MTX - Golimumab 50mg + MTX - Golimumab 100mg + Placebo - Placebo + MTX
Rescue therapy (number of patients)	92
Follow-up time	24 weeks
Primary endpoint	ACR20 at week 14, HAQ-DI at week 24
Secondary endpoints	ACR50, ACR70, ACR90, ACR-N, DAS28, EULAR
JADAD score	5
Comment	

Table 28 Keystone 2008, certolizumab

Examination	phase III, multicenter, randomized, double-blind, placebo-controlled, parallelgroup trial
Number of patients	982

Inclusion criteria	- at least 18 years of age and had a diagnosis of RA, as defined by the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 criteria (11) for 6 months prior to screening but for 15 years Active disease was defined as 9 tender and 9 swollen joints at screening and at baseline, with either an erythrocyte sedimentation rate (ESR; Westergren) 30 mm/ hour or a C-reactive protein (CRP) level 15 mg/liter. - required to have received MTX for 6 months, with a stable dosage of 10 mg/week for 2 months prior to baseline
Exclusion criteria	- diagnoses of any other inflammatory arthritis or a secondary noninflammatory arthritis that could have interfered with our evaluation of the effects of certolizumab pegol on RA - patients with a history of tuberculosis or a chest radiograph showing active or latent tuberculosis - patients with positive findings on a purified protein derivative (PPD) skin test were excluded, unless the PPD positivity was associated with previous vaccination with BCG (PPD positive by local standard) - had a history of malignancy, demyelinating disease, blood dyscrasias, or severe, progressive, and/or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease - had received any biologic therapy within 6 months (or had received etanercept and/or anakinra within 3 months) of baseline and/or any previous biologic therapy that resulted in a severe hypersensitivity or anaphylactic reaction were excluded, as were patients who had previously failed to respond to treatment with an anti-TNF agent
Therapy	- Certolizumab 400 mg + MTX - Certolizumab 200 mg + MTX - Placebo + MTX
Rescue therapy (number of patinets)	
Follow-up time	52 weeks
Primary endpoint	ACR20 at week 24, total Sharp score at week 52
Secondary endpoints	total Sharp score at week 24, HAQ-DI at weeks 24 and 52, ACR20 at week 52, ACR50 and ACR70 at weeks 24 and 52, mean changes from baseline in erosion and joint space narrowing scores, swollen (n 66 joints) and tender (n 68 joints) joint counts, physician's and patient's global assessments of disease activity, patient's assessment of arthritis pain, physical function (according to the HAQ DI), the Disease Activity Score 28-joint assessment (DAS28), the ESR, and the CRP level
JADAD score	5
Comment	

Table 29 Keystone 2004, adalimumab

Examination	double-blind, parallel-group, placebo-controlled study
Number of patients	619
Inclusion criteria	- 18 years of age or older, had active RA diagnosed according to the 1987 revised American College of Rheumatology (ACR; formerly, American Rheumatism Association) criteria, and had 9 tender joints (of 68 evaluated), 6 swollen joints (of 66 evaluated), a C-reactive

	protein concentration 1 mg/dl, and either rheumatoid factor positivity or at least 1 joint erosion on radiographs of the hands and feet - required to have been on MTX therapy for 3 months at a stable dose of 12.5–25 mg/week (or 10 mg/week in patients intolerant to MTX) for 4 weeks
Exclusion criteria	- prior use of anti-CD4 antibody therapy or TNF antagonists, a history of an active inflammatory arthritide other than RA, a history of active listeriosis or mycobacterial infection, a history of lymphoma or leukemia or other malignancy besides nonmelanoma skin cancer within 5 years, a major episode of infection (i.e., infections requiring hospitalization, treatment with intravenous antibiotics within 30 days prior to screening, or oral antibiotics within 14 days prior to screening), any uncontrolled medical condition, and pregnancy or breastfeeding
Therapy	- Adalimumab 40mg every other week + MTX - Adalimumab 20mg weekly + MTX - Placebo + MTX
Rescue therapy (number of patients)	(nem vagyok benne biztos, h az az ág a rescue, amit ide írok) 48
Follow-up time	52 weeks
Primary endpoint	ACR20 at week 24, total Sharp score at week 52, HAQ at week 52
Secondary endpoint	
JADAD score	3
Comment	

Table 30 Klareskog 2004, etanercept

Examination	double-blind, randomised study
Number of patients	682 treated
Inclusion criteria	- aged 18 years or older with disease duration of 6 months to 20 years who had active, adult-onset rheumatoid arthritis (American College of Rheumatology [ACR] functional class I–III), defined as ten or more swollen and 12 or more painful joints and at least one of the following: erythrocyte sedimentation rate 28 mm/h or greater; plasma C-reactive protein 20 mg/L or greater; or morning stiffness for 45 min ormore - should also have had a less than satisfactory response at the discretion of the investigator to at least one disease-modifying antirheumatic drug other than methotrexate
Exclusion criteria	- had previously received etanercept or other TNF antagonists -previous treatment with immunosuppressive drugs within 6 months of screening; use of any investigational drug or biological agent within 3 months of screening; any other disease-modifying antirheumatic drug or corticosteroid injection within 4 weeks of baseline visit; and presence of relevant comorbidity, including active infections
Therapy	- Etanercept (25mg twice a week and oral placebo once a week) - Etanercept + MTX (combination of 25 mg subcutaneous etanercept injections twice a week and oral methotrexate capsules once a week) - Methotrexate only (7·5 mg escalated to 20 mg oral capsules once a week within 8 weeks if patients had any painful or swollen joints,12 and placebo subcutaneous injections twice a week)
Rescue therapy (number of patients)	
Follow-up time	52 weeks

Primary endpoint	The primary efficacy endpoint was the numeric index of the ACR response (ACR-N) area under the curve (AUC) over the first 24 weeks
Secondary endpoint	ACR20, ACR50, ACR70, DAS28
JADAD score	5
Comment	

Table 31 Kremer 2003, abatacept

Examination	randomized, double-blind, placebo-controlled study
Number of patients	339
Inclusion criteria	- 18 to 65 years of age who met the ACR criteria for rheumatoid arthritis and were in functional class I, II, or III - active disease, characterized by 10 or more swollen joints, 12 or more tender joints, and C-reactive protein levels of at least 1 mg per deciliter (upper limit of the normal range, 0.4) - had to have been treated with methotrexate (10 to 30 mg weekly) for at least 6 months and to have received a stable dose for 28 days before enrollment - all other disease-modifying antirheumatic drugs discontinued
Exclusion criteria	- women who were nursing or pregnant
Therapy	- abatacept 10mg/kg + MTX - abatacept 2mg/kg + MTX - Placebo + MTX
Rescue therapy (number of patients)	
Follow-up time	26 week
Primary endpoint	ACR20 at week 26
Secondary endpoints	ACR50, ACR70
JADAD score	5
Comment	

Table 32 Kremer 2006, abatacept

Examination	multicenter, randomized, double-blind, placebocontrolled trial
Number of patients	652
Inclusion criteria	- at least 18 years of age, had had rheumatoid arthritis for at least 1 year, and met the American Rheumatism Association criteria for rheumatoid arthritis - must have been treated with methotrexate (15 mg/wk) for 3 months or longer, with a stable dose for 28 days before enrollment - required patients to undergo a washout of all other disease-modifying antirheumatic drugs at least 28 days before randomization. - required to have 10 or more swollen joints, 12 or more tender joints, and C-reactive protein levels of 10.0 mg/L or greater (normal range, 1.0 mg/L to 4.0 mg/L) while receiving methotrexate - required tuberculin skin testing before randomization
Exclusion criteria	- a positive tuberculin skin test result unless they had completed treatment for latent tuberculosis before enrollment
Therapy	- Abatacept 10mg/kg + MTX - Placebo + MTX
Rescue therapy (number of patients)	
Follow-up time	1 year
Primary endpoint	ACR20 at 6 months, clinically meaningful improvements in physical function, and change from baseline in joint erosion score at 1 year

Secondary endpoint	ACR50, ACR70 at 6 months and all ACR responses at 1 year, DAS28
JADAD score	5
Comment	

Table 33 Kremer 2010, golimumab

Examination	Phase III Randomized, Double-Blind, Placebo-Controlled Study
Number of patients	643
Inclusion criteria	- adults with a diagnosis of RA, as defined by the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria, in whom disease remained active despite receiving treatment with MTX for 3 months prior to screening and being treated with stable dosages of MTX (15–25 mg/week) for 4 weeks prior to screening. Persistent active disease was defined as 4 swollen joints and 4 tender joints and 2 of the following criteria at baseline and/or the time of screening: C-reactive protein (CRP) level of 1.5 mg/dl or an erythrocyte sedimentation rate (ESR) of 28 mm/hour according to the Westergren method, morning stiffness lasting 30 minutes, bone erosion by radiography and/or magnetic resonance imaging, or positivity for anti–cyclic citrullinated peptide or rheumatoid factor
Exclusion criteria	- receipt of infliximab, alefacept or efalizumab within 3 months, treatment with etanercept or adalimumab within 2 months, or treatment with anakinra within 4 weeks prior to the first receipt of the study agent excluded patients, as did any prior receipt of rituximab, abatacept, or natalizumab
Therapy	- Golimumab 4mg/kg + MTX - Golimumab 2mg/kg + MTX - Golimumab 4mg/kg - Golimumab 2mg/kg - Placebo + MTX
Rescue therapy (number of patients)	108
Follow-up time	24 week
Primary endpoint	ACR50 at week 14
Secondary endpoints	ACR50 at week 24, ACR20 at week 14, DAS-CRP at week 14, PCS at week 14
JADAD score	5
Comment	

Table 34 Maini 1999, infliximab

Examination	an international double-blind placebo-controlled phase III clinical trial
Number of patients	428
Inclusion criteria	- had been diagnosed with rheumatoid arthritis according to the 1987 American College of Rheumatology criteria and had evidence of active disease despite treatment with methotrexate (six or more swollen and tender joints plus two of: morning stiffness greater than or equal to 45 min, erythrocyte sedimentation rate greater than 28 mm/h, C-reactive protein greater than 2 mg/dL - must also have been receiving oral or parenteral methotrexate for at least 3 months with no break in treatment of more than 2 weeks during this period. The methotrexate dose must have been stable at 12·5 mg/week or more, for at least 4 weeks before screening and the patient must have been on a stable dose of folic acid for the same

	period. Patients using oral corticosteroids (10 mg/kg or less prednisone equivalent) or non-steroidal anti-inflammatory drugs (NSAIDs) must have been on a stable dose for at least 4 weeks before screening: if a patient was not using such drugs, the patient must not have received either drug for at least 4 weeks before screening. The screening laboratory tests must have met the following criteria: haemoglobin 5·3 mmol/L or more, white blood cells 3·5_109/L or more, neutrophils 1·5_109/L, platelets 100_109/L or more, serum aminotransferase and alkaline phosphatase concentration 2 times or less the upper limit of normal, and serum creatinine 150 _mol/L or less
Exclusion criteria	- had little or no ability for self-care; any current inflammatory condition with signs and symptoms that might confound the diagnosis (eg, connective tissue disease or Lyme disease); used a DMARD other than methotrexate or received intraarticular, intramuscular, or intravenous corticosteroids in the 4 weeks before screening; received any other agent to reduce tumour necrosis factor or had any previous use of cyclophosphamide, nitrogen mustard, chlorambucil, or other alkylating agents; or a history of known allergies to murine proteins - had had infected joint prosthesis during the previous 5 years; serious infections, such as hepatitis, pneumonia, pyelonephritis in the previous 3 months; any chronic infectious disease such as renal infection, chest infection with bronchiectasis or sinusitis; active tuberculosis requiring treatment within the previous 3 years; opportunistic infections such as herpes zoster within the previous 2 months; any evidence of active cytomegalovirus; active *Pneumocystis carinii*; or drug-resistant atypical mycobacterial infection - current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease; a history of lymphoproliferative disease including lymphoma or signs suggestive of disease, such as lymphadenopathy of unusual size or location (ie, lymph nodes in the posterior triangle of the neck, infraclavicular epitrochlear, or periaortic areas); splenomegaly; any known malignant disease except basal cell carcinoma currently or in the past 5 years
Therapy	- Infliximab 10mg/kg every 8 week + MTX - Infliximab 10mg/kg every 4 week + MTX - Infliximab 3mg/kg every 8 week + MTX - Infliximab 3mg/kg every 4 week + MTX - Placebo + MTX
Rescue therapy (number of patients)	0
Follow-up time	30 week
Primary endpoint	ACR20 at week 30
Secondary endpoints	ACR50, ACR70, reduction in individual measurements of disease activity, and a general health assessment
JADAD score	5
Comment	

Table 35 Miyasaka 2008, adalimumab

Examination	Phase II/III, multicenter, double-blind, placebo controlled trial
Number of patients	352
Inclusion criteria	- male and female patients aged 20 years or older - met the American College of Rheumatology (ACR) criteria for

	active RA, had failed treatment with at least one prior disease-modifying antirheumatic drug (DMARD), and had C10 swollen joints and C12 tender joints (excluding distal interphalangeal joints) at both the screening visit and baseline visit. Patients also had a C-reactive protein (CRP) concentration C2 mg/dl - must have discontinued DMARDs at least 28 days prior to study - negative pregnancy test and use of reliable contraception were mandatory for women of childbearing potential
Exclusion criteria	- acute inflammatory joint diseases other than RA, active Listeria or tuberculosis, lymphoma, or leukemia, or any malignancy except for successfully treated nonmetastatic basal-cell carcinoma of the skin. - positive serology for anti-human immunodeficiency virus antibody, hepatitis B virus surface antigen, or anti-hepatitis C virus antibody, ongoing or active infection, advanced or poorly controlled diabetes, or central nervous system demyelinating disorders
Therapy	- Adalimumab 20mg every other week - Adalimumab 40mg every other week - Adalimumab 80mg every other week - Placebo every other week
Rescue therapy (number of patients)	104 a szövegben 107-et írnak
Follow-up time	24 week
Primary endpoint	ACR20 at week 24
Secondary endpoints	The comparison between ACR20 response rates at week 24 for the adalimumab 20 mg group and the placebo group. Additional secondary efficacy endpoints included ACR20 response rate at Week 12; ACR50 and ACR70 response rates at Weeks 12 and 24; individual components of the ACR response at Weeks 0 12, and 24; and the Health Assessment Questionnaire Disability Index at Weeks 0 12, and 24.
JADAD score	5
Comment	

Table 36 Moreland 1999, etanercept

Examination	Randomized, double-blind, placebo-controlled trial with blinded joint assessors
Number of patients	234
Inclusion criteria	- adults who were at least 18 years of age, met the American Rheumatism Association's diagnostic criteria for rheumatoid arthritis, and were in functional class I, II, or III - required to have had an inadequate response to one to four DMARDs (such as azathioprine, methotrexate, sulfasalazine, penicillamine, hydroxychloroquine, or oral or injectable gold); an inadequate response was defined as discontinuation of therapy because of lack of effect - if patients were receiving DMARDs, they were required to complete a DMARD washout period that lasted at least 1 month before starting study drug treatment; no DMARDs were permitted during the study - had to have active disease at enrollment (before the DMARD washout period), defined as 12 or more tender joints, 10 or more swollen joints, and at least one of the following: erythrocyte sedimentation rate of at least 28 mm/h, C-reactive protein level greater than 20 mg/L, or morning stiffness for at least 45 minutes - all patients were required to have aminotransferase levels no greater

	than twice the upper limit of normal, a hemoglobin level of 85 g/dL or greater, a platelet count of at least 125 000 cells/mm", a leukocyte count of 3500 cells/mm" or higher, and a serum ereatinine level of 176.8 jamol/L (2mg/dL) or less
Exclusion criteria	- intra-articular corticosteroids were not permitted during the study or beginning 4 weeks before enrollment
Therapy	- Etanercept 25mg twice a week - Etanercept 10mg twice a week - Placebo
Rescue therapy (number of patients)	
Follow-up time	26 weeks
Primary endpoint	ACR20, ACR50 at 3 and 6 months
Secondary endpoint	ACR70 response at 3 and 6 months and percentage change from baseline at 3 and 6 months in the following: tender joint count, swollen joint count, duration of morning stiffness, patient's global assessment, physician's global assessment, patient's assessment of pain, quality of life, erythrocyte sedimentation rate, and C-reactive protein level
JADAD score	5
Comment	

Table 37 Nishimoto 2007, tocilizumab

Examination	a multi-centre, x ray reader-blinded, randomised, controlled trial
Number of patients	306
Inclusion criteria	- age 20 years and fulfilled the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria for the classification of RA,23 with a disease duration of >6 months and ,5 years. In addition, they had >6 tender joints (of 49 evaluated), >6 swollen joints (of 46 evaluated), an erythrocyte sedimentation rate (ESR) of >30 mm/h and C-reactive protein (CRP) of >20 mg/l. All candidates had an inadequate response to at least one disease modifying antirheumatic drug (DMARD) or immunosuppressant. - had white blood cell counts of at least 3.56109/l, lymphocyte counts of at least 0.56109/l and platelet counts of at least 1006109/l at enrolment - sexually active premenopausal women were required to have a negative urine pregnancy test at the entry and to use effective contraception during the study period
Exclusion criteria	- had a medical history of a serious allergic reaction, significant concomitant diseases, or an active intercurrent infection requiring medication within 4 weeks before the first dose
Therapy	- Tocilizumab 8mg/kg every 4 weeks - DMARD
Rescue therapy (number of patients)	
Follow-up time	52 weeks
Primary endpoint	radiological scores*
Secondary endpoint	
JADAD score	5

Comment	*radiographic endpoints, such as TSS, erosion score and joint space narrowing score, were assessed with a rank transformed analysis of covariance (ANCOVA) on the change scores that included factors for baseline score and baseline disease duration

Table 38 Nishimoto 2009, tocilizumab

Examination	multi-center, randomized, blinded, double-dummy trial
Number of patients	125
Inclusion criteria	- patients were between 20 and 75 years old, fulfilled the American college of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria for the classification of RA, with disease duration of more than 6 months - candidates were treated with MTX 8 mg/week for at least 8 weeks until enrolment. They all had C6 tender joints (of 49 evaluated), C6 swollen joints (of 46 evaluated), ESR of C30 mm/h or CRP of C10 mg/l at enrolment - patients had white blood cell counts C3.5 9 109/l, lymphocyte counts C0.5 9 109/l and platelet count of at least the lower limit of normal as defined by the respective local laboratory used - sexually active premenopausal women were required to have a negative urine pregnancy test at the entry to the study and to use effective contraception during the study period
Exclusion criteria	- had functional class IV using Steinbrocker's criteria aspartate transaminase (AST), alanine transaminase (ALT) and serum creatinine C1.5-fold the upper limit of normal, were HBs antigen and/ or HCV antibody positive, had pulmonary fibrosis or active pulmonary disease, a history of serious adverse drug reaction to MTX, concomitant pleural effusion, ascites, varicella infection, or were excessive users of alcohol on a regular basis - had significant cardiac, blood, respiratory system, neurologic, endocrine, renal, hepatic, or gastrointestinal disease, or had an active infection requiring medication within 4 weeks before the first dose or medical history of a serious allergic reaction
Therapy	- Tocilizumab 8mg/kg every 4 weeks + MTX placebo - Tocilizumab placebo + Methotrexate 8mg/week
Rescue therapy (number of patients)	
Follow-up time	24 weeks
Primary endpoint	ACR20 at week 24
Secondary endpoint	
JADAD score	3
Comment	

Table 39 Schiff 2008, abatacept

Examination	phase III, randomised, double-blind, double-dummy, placebo- and active (infliximab)-controlled multi-center study
Number of patients	431
Inclusion criteria	- met the American College of Rheumatology (ACR) criteria for RA, were at least 18 years of age, had RA for at least 1 year,4 and had an inadequate response to MTX, as demonstrated by ongoing active disease (at randomisation> 10 swollen joints,> 12 tender joints, and C-reactive protein (CRP) levels> 1 mg/dl using a high sensitivity

	assay (upper limit of the normal range, 0.5)) - had received MTX> 15 mg/week for> 3 months prior to randomisation (stable for at least 28 days) and washed out all DMARDs (> 28 days prior) except for MTX - no prior experience of abatacept or anti-TNF therapy was permitted
Exclusion criteria	
Therapy	- abatacept 10mg/kg + MTX - infliximab 3mg/kg every 8 weeks + MTX - placebo + MTX
Rescue therapy (number of patients)	0
Follow-up time	52 weeks
Primary endpoint	DAS28 with abatacept vs. placebo
Secondary endpoint	DAS28 with infliximab vs. placebo; DAS28 with abatacept vs infliximab; EULAR; 6 low disease activity score (LDAS; DAS28 (ESR), DAS28, (ESR)-defined remission (DAS28 (ESR); ACR 20, 50 and 70 responses; HAQ-DI; response rates and mean changes in the physical and mental component summary (PCS and MCS, respectively) scores; and eight subscales of the SF-36
JADAD score	5
Comment	

Table 40 Smolen 2008, tocilizumab

Examination	phase III, three arm, randomised, double-blind, placebo-controlled, parallel group, international study
Number of patients	623
Inclusion criteria	- adult patients with moderate to severe active rheumatoid arthritis (diagnosed according to American College of Rheumatology [ACR] criteria) of more than 6 months'duration who had an inadequate response to methotrexate were recruited - active disease was defi ned by a swollen joint count of 6 or more plus a tender joint count of 8 or more and C-reactive protein (CRP) over 10 mg/L or ESR of 28 mm/h or more - had to have received methotrexate for 12 weeks or longer before the start of the study (stable dose of 10–25 mg/week for 8 weeks or longer) - all other DMARDs were discontinued before the start of the study: lefl unomide for 12 weeks or more (or ≥4 weeks after 11 days of standard colestyramine washout), anakinra for 1 week or more, etanercept for 2 weeks or longer, and infl iximab or adalimumab for 8 weeks or longer
Exclusion criteria	- other autoimmune diseases or significant systemic involvement secondary to rheumatoid arthritis (eg, vasculitis, pulmonary fi brosis, or Felty's syndrome), functional class IV rheumatoid arthritis, previous or current infl ammatory joint disease other than rheumatoid arthritis, currently active or previous recurrent bacterial, viral, fungal, or other infections including, but not limited to, tuberculosis and atypical mycobacterial disease, clinically signifi cant abnormalities on chest radiograph, hepatitis B and C, and recurrent herpes zoster - had active liver disease, indicated by screening and baseline concentrations of alanine or aspartate aminotransferase of 1· 5 times the upper limit of normal or more, or previous unsuccessful treatment with an anti-TNF agent (ie, lack of effi cacy or signifi cant safety issues; terminations due to cost or injection discomfort were not

	excluded)
Therapy	- Tocilizumab 8mg/kg every 4 week + MTX (10-25mg) weekly - Tocilizumab 4mg/kg every 4 week + MTX (10-25mg) weekly - Placebo every 4 week + MTX (10-25mg) weekly
Rescue therapy (number of patients)	118
Follow-up time	24 weeks
Primary endpoint	ACR20 at week 24
Secondary endpoint	ACR50, ACR70, DAS28, DAS (remission), EULAR at week 24
JADAD score	5
Comment	

Table 41 Smolen 2009, golimumab

Examination	a multicentre, randomised, double-blind, placebo-controlled, phase III trial
Number of patients	461
Inclusion criteria	- aged 18 years or older, and had been diagnosed with active rheumatoid arthritis (persistent disease activity with at least four swollen and four tender joints), according to the criteria of the American College of Rheumatology (ACR), at least 3 months before screening - must have been treated with at least one dose of a TNFα inhibitor (etanercept, adalimumab, or infl iximab), the last dose of which must have been given at least 8 weeks (adalimumab or etanercept) or 12 weeks (infl iximab) before the first dose of the study drug - patients receiving such drugs must have tolerated the dose for at least 12 weeks, and the dose must have been stable for 4 weeks before the first dose of study drug
Exclusion criteria	- had inflammatory diseases other than rheumatoid arthritis; had a serious adverse reaction to a previous TNFα inhibitor (judged by the investigator); had ever received natalizumab or rituximab; had received anakinra less than 4 weeks, or alefacept or efalizumab less than 3 months before the first dose of study drug; had ever received cytotoxic drugs; had a history of latent or active granulomatous infection, except latent tuberculosis, that was treated prophylactically in the past 3 years; had a BCG vaccination less than 12 months before screening; had an opportunistic infection less than 6 months before screening; had a serious infection (judged by the investigator) less than 2 months before screening; had a history of chronic infection, demyelinating disease, congestive heart failure, or severe, progressive, uncontrolled renal, hepatic, haematological, gastro intestinal, endocrine, pulmonary, cardiac, neurological, psychiatric, or cerebral disease; or had a transplanted organ or a malignancy in the past 5 years
Therapy	- Golimumab 100mg every 4 weeks - Golimumab 50mg every 4 weeks - Placebo every 4 weeks
Rescue therapy (number of patients)	113
Follow-up time	24 weeks
Primary endpoint	ACR20, the number of tender (0–68) and swollen (0–66) joints, and at least three of either patient assessment of pain (0–10 cm, visual analogue scorepatient global assessment of disease activity (0–10 cm, VAS, 0 indicates no disease), physician global assessment of disease

	activity (0–10 cm, VAS), patient assessment of physical function (0–3, health assessment questionnaire disability index [HAQ-DI], 0 indicates no disability),12 or C-reactive protein concentration (normal range according to the central laboratory 0–6 mg/L) at week 14
Secondary endpoints	ACR20 at week 24, ACR50 and ACR70 at weeks 14 and 24; numeric index of the ACR response18 at weeks 14 and 24; DAS28 at weeks 14 and 24; HAQ-DI scores at weeks 14 and 24; fatigue score at weeks 14 and 24; DAS28 response according to EULAR and DAS28 remission
JADAD score	5
Comment	

Table 42 Smolen 2008, certolizumab

Examination	an international, multicentre, phase 3, randomised, double-blind, placebo-controlled study
Number of patients	619
Inclusion criteria	- aged >18 years with a diagnosis of RA, defined by American College of Rheumatology (ACR) 1987 criteria,19 of >6 months' duration but not longer than 15 years, with active disease at screening and baseline. Patients had to have received prior MTX for >6 months (stable dose >10 mg/week for >2 months before baseline)
Exclusion criteria	- had received any biological agent for RA within 6 months before enrolment (3 months for etanercept and anakinra), had received previous treatment with a biological agent resulting in a severe hypersensitivity or anaphylactic reaction, or had not initially responded to previous anti-TNF therapy - patients with history of, or positive chest x-ray findings for, tuberculosis, or a positive purified protein derivative (PPD) skin test (defined as positive indurations per local medical practice)
Therapy	- Certolizumab 400mg + MTX at weeks 0, 2, 4 - Certolizumab 200mg + MTX - Placebo + MTX every 2 weeks
Rescue therapy (number of patients)	214
Follow-up time	24 weeks
Primary endpoint	ACR20 at week 24
Secondary endpoints	ACR50, ACR70, mTSS and individual ACR core set variables at week 24
JADAD score	3
Comment	

Table 43 Tak 2011, rituximab

Examination	double-blind, randomized, controlled, phase III study
Number of patients	748
Inclusion criteria	- aged 18–80 years with RA diagnosed according to the revised 1987 American College of Rheumatology (ACR) criteria. Disease duration was ≥8 weeks but ≤4 years. Patients were not to have received previous treatment with MTX and were to have active disease defi ned as a swollen joint count (66 joints) and tender joint count (68 joints) both ≥8 at screening and baseline, and C-reactive protein (CRP) ≥1.0 mg/dl
Exclusion criteria	
Therapy	- Rituximab 1000mg twice a week + MTX

	- Rituximab 500mg twice a week + MTX - Placebo + MTX
Rescue therapy (number of patients)	
Follow-up time	52 weeks
Primary endpoint	change in total Sharp score from baseline to week 52
Secondary endpoint	
JADAD score	5
Comment	

Table 44 VandePutte 2004, adalimumab

Examination	double blind, placebo controlled, phase III trial
Number of patients	544
Inclusion criteria	- met the diagnostic criteria for RA established by the American College of Rheumatology (ACR), treatment with at least one DMARD had previously failed, and they had active disease defined as >12 tender joints based on a 68 joint assessment, >10 swollen joints based on a 66 joint evaluation, and either an erythrocyte sedimentation rate (ESR) >28 mm/1st h or a serum C reactive protein (CRP) concentration >20 mg/l - negative pregnancy test and the use of a reliable contraceptive method were mandatory in women of childbearing potential
Exclusion criteria	- joint surgery within 2 months before screening or infection requiring admission to hospital or treatment with intravenous (iv) antibiotics within 1 month before screening - had received treatment with either an intra-articular or intramuscular corticosteroid within 1 month before the study or an investigational small molecule drug or biological agent within 2 months or 6 months before screening, respectively - patients with impaired renal or hepatic function, or a history of tuberculosis as shown by radiographs
Therapy	- Adalimumab 40mg weekly - Adalimumab 40mg every other week - Adalimumab 20mg weekly - Adalimumab 20mg every other week - Placebo
Rescue therapy (number of patients)	
Follow-up time	26 weeks
Primary endpoint	ACR20
Secondary endpoints	ACR50, ACR70, EULAR, HAQ-DI and improvements in ACR core components (patient global assessment of disease activity, physician global assessment of disease activity, patient assessment of pain, the Disability Index of the Health Assessment Questionnaire (HAQ DI), and serum levels of CRP, changes in the disease activity score 28 (DAS28), a composite score (score 2–10) defined by criteria established by the European League Against Rheumatism (EULAR)
JADAD score	5
Comment	

Table 45 Weinblatt 2006, abatacept

Examination	multinational, multicenter, randomized, double-blind, 2-arm, parallel-dosing trial
Number of patients	1441

Inclusion criteria	- men and women at least 18 years of age who met the 1987 American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria for the diagnosis of RA and the 1991 ACR criteria for RA functional classes I, II, III, or IV Patients had to have active disease despite receiving background DMARDs and/or biologic therapy, warranting additional therapy at the discretion of the investigator. - required to have been receiving 1 biologic and/or nonbiologic DMARD approved for RA for at least 3 months, and at a stable dose for at least 28 days prior to day 1 of the trial - patients with stable medical conditions such as congestive heart failure (CHF), asthma, chronic obstructive pulmonary disease (COPD), and diabetes mellitus were included
Exclusion criteria	- had unstable or uncontrolled renal, endocrine, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, or neurologic diseases, or any autoimmune disorder other than RA as the main diagnosis - active or chronic recurrent bacterial infections unless treated and resolved, active herpes zoster infection within the previous 2 months, hepatitis B or hepatitis C virus infection, and active or latent tuberculosis (as assessed via chest radiography and tuberculin testing) unless appropriately treated - pregnant or nursing women
Therapy	- Abatacept 10mg/kg + DMARD - Placebo + DMARD
Rescue therapy (number of patients)	
Follow-up time	1 year
Primary endpoint	evaluate the safety
Secondary endpoints	ACR20, ACR50, ACR70, HAQ, patient's global assessment of disease activity, patient's global assessment of pain, and physician's global assessment of disease activity were all assessed using a 100-mm VAS
JADAD score	5
Comment	

Table 46 Weinblatt 1999, etanercept

Examination	multicenter, randomized, double-blind trial
Number of patients	89
Inclusion criteria	- at least 18 years of age and fulfilled the 1987 criteria for rheumatoid arthritis of the American Rheumatism Association were in functional class I, II, or III according to the revised criteria of the American College of Rheumatology (ACR) and had active disease, as manifested by at least six joints that were swollen and six that were tender at the time of enrollment. Before receiving the study drugs, all the patients had been taking methotrexate for at least six months, and at a stable dose of 15 to 25 mg per week for the last four weeks (weekly doses as low as 10 mg were acceptable for patients who could not tolerate higher doses). All patients received folic acid or folinic acid to mitigate the toxic effects of methotrexate. - had platelet counts of at least 125,000 per cubic millimeter, serum creatinine levels of no more than 2 mg per deciliter (177 µmol per liter), white-cell counts of at least 3500 per cubic millimeter, serum aspartate and alanine aminotransferase levels no more than 1.2 times

	the laboratory's upper limit of normal, hemoglobin levels of at least 8.5 g per deciliter, stable hemoglobin levels for at least six months in patients with levels of less than 10 g per deciliter, and negative serologic results on tests for hepatitis B surface antigen and hepatitis C antibody - patients discontinued therapy with sulfasalazine and hydroxychloroquine at least two weeks before starting to take the study drug and disease-modifying antirheumatic drugs other than methotrexate at least four weeks before
Exclusion criteria	
Therapy	- Etanercept 25mg twice weekly + MTX - Placebo + MTX
Rescue therapy (number of patients)	
Follow-up time	24 weeks
Primary endpoint	ACR20 at week 24
Secondary endpoint	ACR 20 at week12 and the proportions who met the ACR 50 and ACR70 at 12 and 24 weeks, individual measures of disease activity, such as numbers of swollen and tender joints and physician's assessment, at 12 and 24 weeks
JADAD score	3
Comment	

Table 47 Weinblatt 2003, adalimumab

Examination	randomized, double-blind, placebo-controlled trial
Number of patients	271
Inclusion criteria	- 18 years of age or older and had RA that was diagnosed according to the 1987 revised criteria of the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) Active disease was defined as the presence of at least 9 tender joints (of 68 joints evaluated) and 6 swollen joints (of 66 joints evaluated). Additionally, participants must have been treated with MTX for a minimum of 6 months and must have been taking a stable weekly dose (12.5–25 mg, or 10 mg if intolerant to higher doses) for at least 4 weeks before entering the study. - must have failed treatment with at least 1 DMARD besides MTX, but no more than 4 DMARDs
Exclusion criteria	- had received treatment with anti-CD4 therapy or TNF antagonists, had a history of active listeriosis or mycobacterial infection, and had a major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days prior to screening
Therapy	- Adalimumab 80mg every other week + MTX - Adalimumab 40mg every other week + MTX - Adalimumab 20mg every other week + MTX - Placebo + MTX
Rescue therapy (number of patients)	
Follow-up time	24 weeks
Primary endpoint	ACR20
Secondary endpoint	ACR50, ACR70, improvements in ACR core set of disease activity measures for RA clinical trials, as follows: tender joint count, swollen joint count, patient's assessment of pain, patient's global assessment of disease activity, HAQ-DI, and serum levels of C-reactive protein,

	FACIT, proMMP-1and proMMP-3
JADAD score	3
Comment	

Table 48 Westhovens 2009, abatacept

Examination	multi-national, randomised, doubleblind
Number of patients	509
Inclusion criteria	- 18 years of age or older, with RA for 2 years or less, at least 12 tender and 10 swollen joints, C-reactive protein (CRP) 0.45 mg/dl or greater, RF and/or anti-CCP2 seropositivity and radiographic evidence of bone erosion of the hands/wrists/feet. Patients were either methotrexate-naive or had previous exposure of 10 mg/week or less for 3 weeks or less, with none administered for 3 months before providing informed consent (there were no requirements relating to the reason for discontinuation of previous methotrexate therapy) - required to practice effective contraceptive measures for the study duration
Exclusion criteria	- women who were pregnant or breastfeeding - had had active Mycobacterium tuberculosis (tuberculosis) requiring treatment within 3 years
Therapy	- Abatacept 10mg/kg + MTX - Placebo + MTX
Rescue therapy (number of patients)	
Follow-up time	2 years
Primary endpoint	DAS28, Genant-modified Sharp score
Secondary endpoint	ACR50, DAS28, MCR, ACR70, Genant-modified Sharp erosion score, joint-space narrowing score, physical function, health-related quality of life (HRQoL)
JADAD score	5
Comment	

Table 49 Westhovens 2006, infliximab

Examination	Randomized, Placebo-Controlled Trial
Number of patients	1084
Inclusion criteria	- had a diagnosis of RA according to the revised criteria of the American College of Rheumatology (ACR; formerly, the American Rheumatism Association), and had active disease despite receiving MTX; patients may or may not have been treated with other concomitant DMARDs. Active RA was defined as the presence of 6 swollen joints and 6 tender joints. At screening, patients were required to have a chest radiograph that showed no evidence of malignancy, infection, fibrosis, or active tuberculosis - must have been receiving MTX for at least 3 months prior to randomization. The MTX dose must have been stable for at least 4 weeks prior to randomization
Exclusion criteria	- had opportunistic infections, serious infections during the 2 months prior to screening, known human immunodeficiency virus infection, active tuberculosis or history of active tuberculosis with inadequate documentation of treatment, evidence of latent tuberculosis and an inability to receive prophylaxis with isoniazid, a history of lymphoproliferative disease or malignancy, or a diagnosis of

	congestive heart failure - if had been treated with an investigational drug (within 3 months or 5 half-lives from the time of screening, whichever was greater), with cyclophosphamide, nitrogen mustard, chlorambucil, or other alkylating agents, with more than 5 mg/kg of cyclosporine, or with any approved or investigational biologic agent (including infliximab) at any time prior to the study, with the exception of approved vaccines for the purpose of immunization
Therapy	- Infliximab 10mg/kg + MTX at weeks 0, 2, 6, and 14 - Infliximab 3mg/kg + MTX at weeks 0, 2, 6, and 14 - Placebo + MTX at weeks 0, 2, 6, and 14
Rescue therapy (number of patients)	
Follow-up time	22 weeks
Primary endpoint	occurrence of serious infections as primary end point through week 22
Secondary endpoints	ACR20, ACR50, ACR70, DAS28
JADAD score	5
Comment	

Table 50 Kim 2007 adalimumab

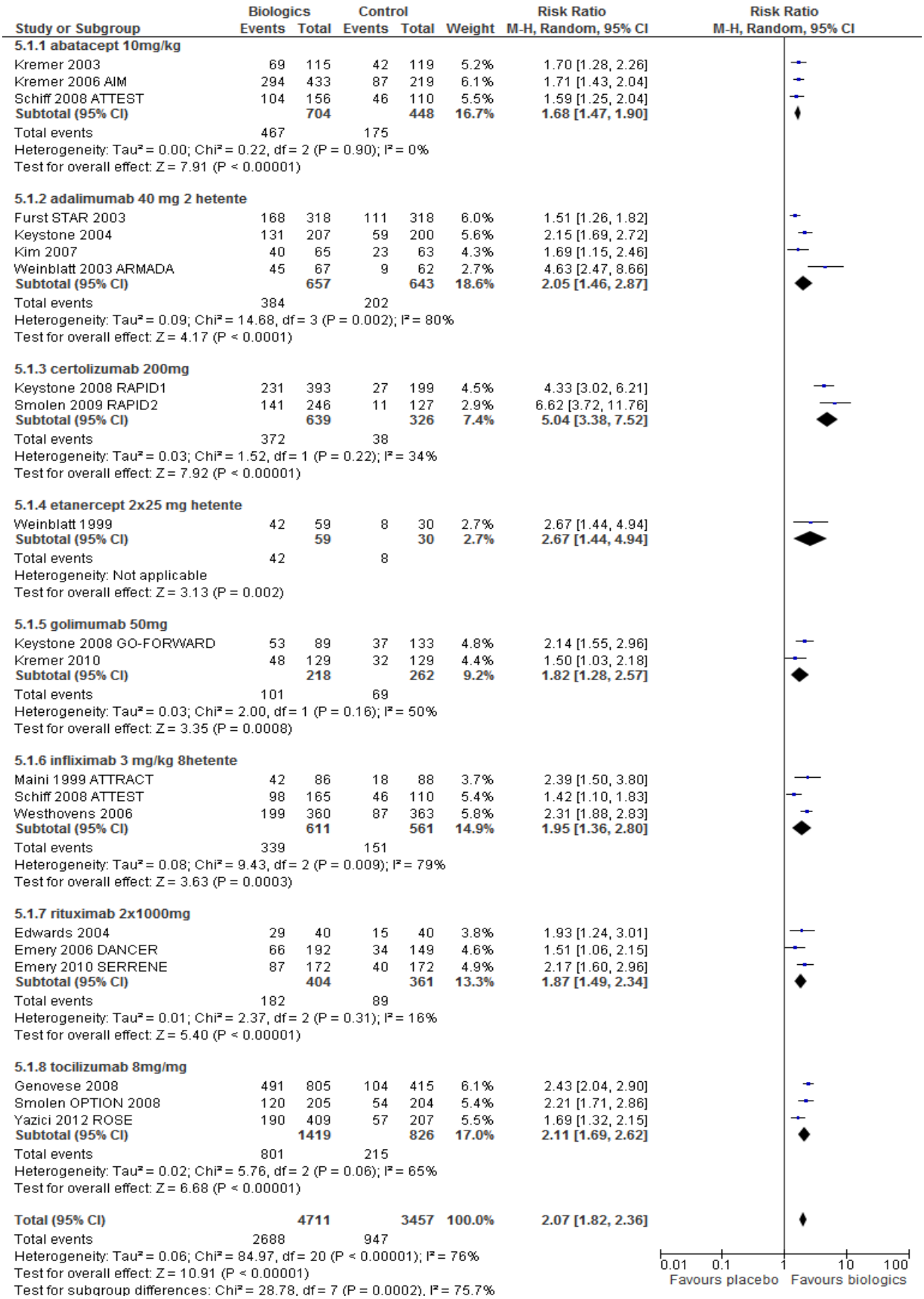
Examination	randomized, double-blind, placebo-controlled, phase III study
Number of patients	128
Inclusion criteria	- 18 years of age or older - met American College of Rheumatology (ACR) criteria for diagnosis of active RA, and had ≥ 6 swollen joints and ≥ 9 tender joints at both screening and baseline visits - had to have received at least one prior DMARD other than MTX but could have had efficacy failures to no more than four standard DMARDs other than MTX - had to have been treated with MTX for at least 6 months and been receiving a stable dosage for at least 4 weeks prior to screening
Exclusion criteria	- acute inflammatory joint diseases other than RA, active *Listeria* or tuberculosis infection; positive serology for human immunodeficiency virus antibody, hepatitis B surface antigen, or hepatitis C antibody; calcified granuloma and/or pleural scarring on chest radiograph
Therapy	- Adalimumab 40 mg every other week - Placebo
Rescue therapy (number of patients)	27
Follow-up time	24 weeks
Primary endpoint	ACR20 compared with the placebo group at week 24
Secondary endpoint	ACR50, ACR70, the percentage of patients achieving improvement in individual ACR core components, including tender joint count, swollen joint count, the Physician's Global Assessment of Disease Activity, the Patient's Global Assessment of Disease Activity, the Patient's Global Assessment of Pain, Disability Index of the Korea Health Assessment Questionnaire (KHAQ), and C-reactive protein concentrations; and the percentage of patients reporting morning stiffness
JADAD score	1
Comment	

Table 51 Yazici 2012 tocilizumab

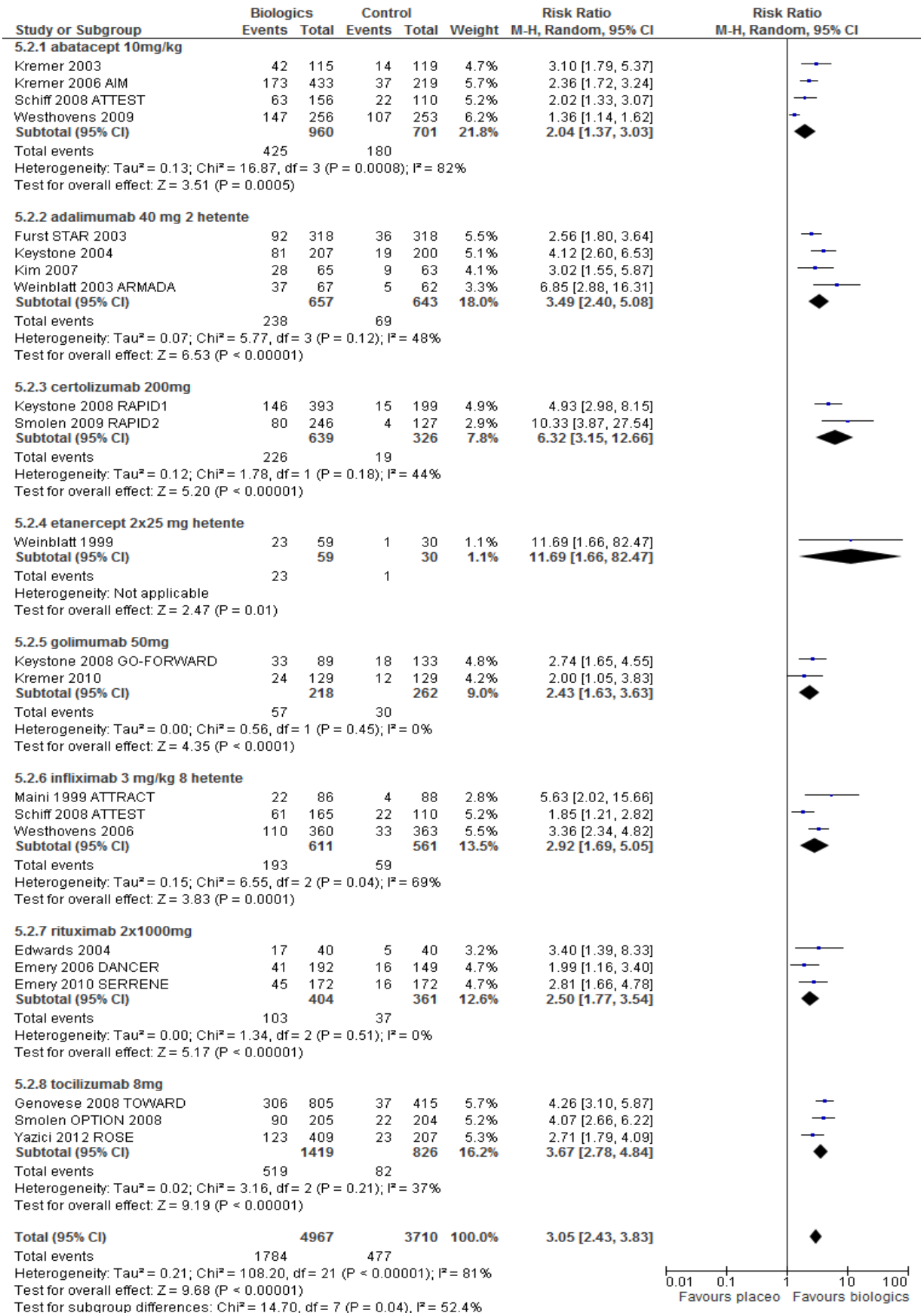
Examination	randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase IIIb clinical trial
Number of patients	614
Inclusion criteria	- adults diagnosed with active RA for at least 6 months who were experiencing an inadequate clinical response to DMARD as determined by the investigator - had six or more swollen joints and six or more tender joints at screening and baseline, and either a C-reactive protein (CRP) level of 95.24 nmol/l or greater or an erythrocyte sedimentation rate (ESR) of 28 mm/h or greater at screening - discontinue previous biological therapy before randomisation
Exclusion criteria	
Therapy	- tocilizumab 8mg/kg every 4 weeks + DMARD - placebo every 4 weeks + DMARD
Rescue therapy (number of patients)	124
Follow-up time	24 weeks
Primary endpoint	ACR50
Secondary endpoint	every 4 weeks to week 24: ACR20/50/70 responses; EULAR responses; DAS28, including proportions of patients with clinically meaningful improvement (change from baseline in DAS28 of ≥1.2) and patients achieving low disease activity (LDA, DAS28 ≤3.2) or clinical remission (DAS28 <2.6) ESR and CRP levels; functional assessment of chronic illness therapy fatigue (FACIT-F) and routine assessment of patient index data (RAPID3) scores (on a scale of 0–10) derived from the multidimensional health assessment questionnaire (MDHAQ)
JADAD score	3
Comment	

8.6 Detailed results from classical direct meta-analysis

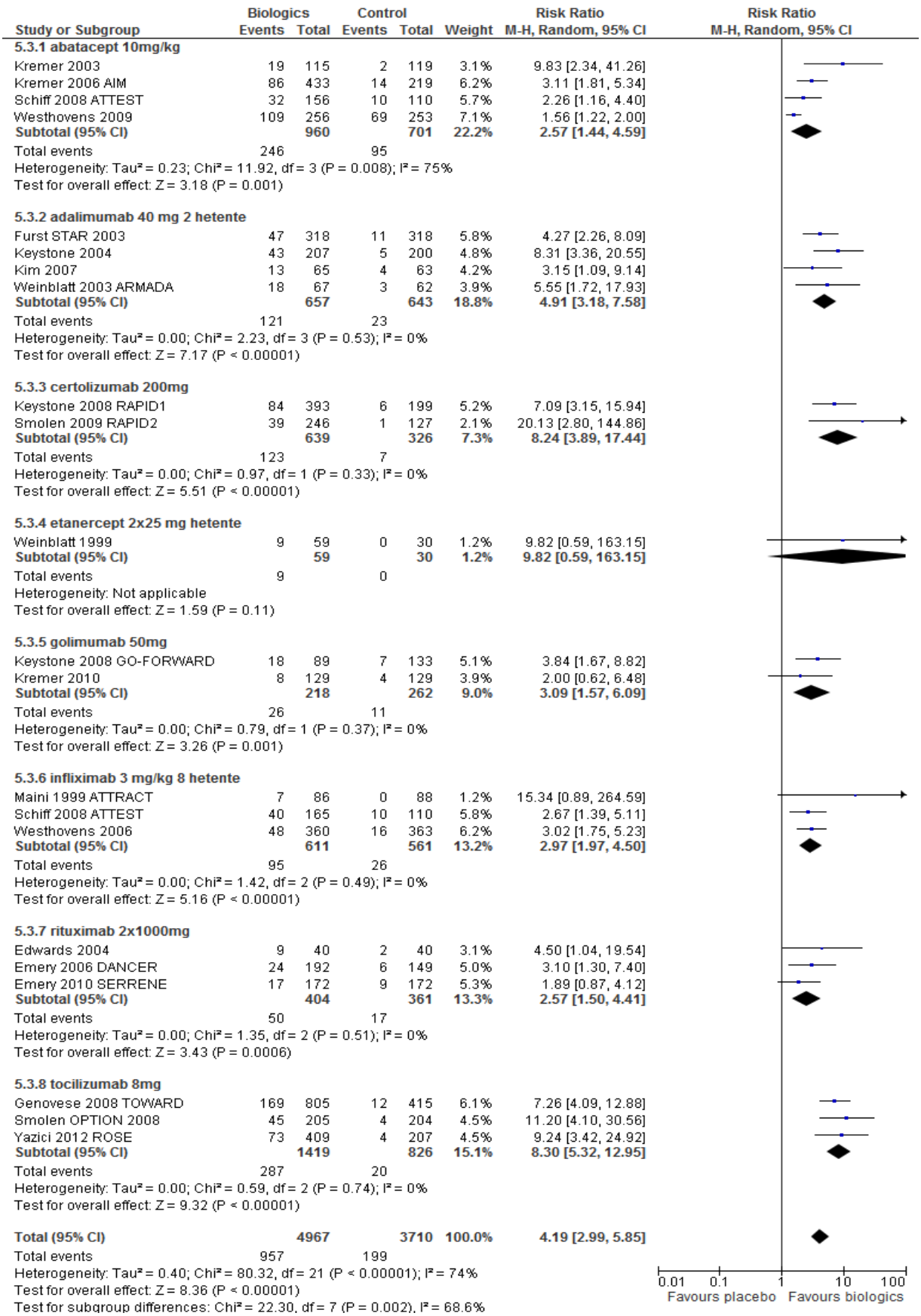
Forest plot of comparison: 5 Efficacy of biological + DMARD at six months in DMARD IR population, outcome: ACR20



Forest plot of comparison: Efficacy of biological + DMARD at six months in DMARD IR population, outcome: ACR50


Biologics
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
5.2.1 abatacept 10mg/kg
Kremer 2003 42 115 14 119 4.7% 3.10 [1.79, 5.37]
Kremer 2006 AIM 173 433 37 219 5.7% 2.36 [1.72, 3.24]
Schiff 2008 ATTEST 63 156 22 110 5.2% 2.02 [1.33, 3.07]
Westhovens 2009 147 256 107 253 6.2% 1.36 [1.14, 1.62]
Subtotal (95% CI) 960 701 21.8% 2.04 [1.37, 3.03]
Total events 425 180
Heterogeneity: Tau² = 0.13; Chi² = 16.87, df = 3 (P = 0.0008); I² = 82%
Test for overall effect: Z = 3.51 (P = 0.0005)
5.2.2 adalimumab 40 mg 2 hetente
Furst STAR 2003 92 318 36 318 5.5% 2.56 [1.80, 3.64]
Keystone 2004 81 207 19 200 5.1% 4.12 [2.60, 6.53]
Kim 2007 28 65 9 63 4.1% 3.02 [1.55, 5.87]
Weinblatt 2003 ARMADA 37 67 5 62 3.3% 6.85 [2.88, 16.31]
Subtotal (95% CI) 657 643 18.0% 3.49 [2.40, 5.08]
Total events 238 69
Heterogeneity: Tau² = 0.07; Chi² = 5.77, df = 3 (P = 0.12); I² = 48%
Test for overall effect: Z = 6.53 (P < 0.00001)
5.2.3 certolizumab 200mg
Keystone 2008 RAPID1 146 393 15 199 4.9% 4.93 [2.98, 8.15]
Smolen 2009 RAPID2 80 246 4 127 2.9% 10.33 [3.87, 27.54]
Subtotal (95% CI) 639 326 7.8% 6.32 [3.15, 12.66]
Total events 226 19
Heterogeneity: Tau² = 0.12; Chi² = 1.78, df = 1 (P = 0.18); I² = 44%
Test for overall effect: Z = 5.20 (P < 0.00001)
5.2.4 etanercept 2x25 mg hetente
Weinblatt 1999 23 59 1 30 1.1% 11.69 [1.66, 82.47]
Subtotal (95% CI) 59 30 1.1% 11.69 [1.66, 82.47]
Total events 23 1
Heterogeneity: Not applicable
Test for overall effect: Z = 2.47 (P = 0.01)
5.2.5 golimumab 50mg
Keystone 2008 GO-FORWARD 33 89 18 133 4.8% 2.74 [1.65, 4.55]
Kremer 2010 24 129 12 129 4.2% 2.00 [1.05, 3.83]
Subtotal (95% CI) 218 262 9.0% 2.43 [1.63, 3.63]
Total events 57 30
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 4.35 (P < 0.0001)
5.2.6 infliximab 3 mg/kg 8 hetente
Maini 1999 ATTRACT 22 86 4 88 2.8% 5.63 [2.02, 15.66]
Schiff 2008 ATTEST 61 165 22 110 5.2% 1.85 [1.21, 2.82]
Westhovens 2006 110 360 33 363 5.5% 3.36 [2.34, 4.82]
Subtotal (95% CI) 611 561 13.5% 2.92 [1.69, 5.05]
Total events 193 59
Heterogeneity: Tau² = 0.15; Chi² = 6.55, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 3.83 (P = 0.0001)
5.2.7 rituximab 2x1000mg
Edwards 2004 17 40 5 40 3.2% 3.40 [1.39, 8.33]
Emery 2006 DANCER 41 192 16 149 4.7% 1.99 [1.16, 3.40]
Emery 2010 SERRENE 45 172 16 172 4.7% 2.81 [1.66, 4.78]
Subtotal (95% CI) 404 361 12.6% 2.50 [1.77, 3.54]
Total events 103 37
Heterogeneity: Tau² = 0.00; Chi² = 1.34, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 5.17 (P < 0.00001)
5.2.8 tocilizumab 8mg
Genovese 2008 TOWARD 306 805 37 415 5.7% 4.26 [3.10, 5.87]
Smolen OPTION 2008 90 205 22 204 5.2% 4.07 [2.66, 6.22]
Yazici 2012 ROSE 123 409 23 207 5.3% 2.71 [1.79, 4.09]
Subtotal (95% CI) 1419 826 16.2% 3.67 [2.78, 4.84]
Total events 519 82
Heterogeneity: Tau² = 0.02; Chi² = 3.16, df = 2 (P = 0.21); I² = 37%
Test for overall effect: Z = 9.19 (P < 0.00001)
Total (95% CI) 4967 3710 100.0% 3.05 [2.43, 3.83]
Total events 1784 477
Heterogeneity: Tau² = 0.21; Chi² = 108.20, df = 21 (P < 0.00001); I² = 81%
Test for overall effect: Z = 9.68 (P < 0.00001)
Test for subgroup differences: Chi² = 14.70, df = 7 (P = 0.04), I² = 52.4%
0.01 0.1 1 10 100
Favours placeo Favours biologics

Forest plot of comparison: 5 Efficacy of biological + DMARD at six months in DMARD IR population, outcome: ACR70


Biologics
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
5.3.1 abatacept 10mg/kg
Kremer 2003 19 115 2 119 3.1% 9.83 [2.34, 41.26]
Kremer 2006 AIM 86 433 14 219 6.2% 3.11 [1.81, 5.34]
Schiff 2008 ATTEST 32 156 10 110 5.7% 2.26 [1.16, 4.40]
Westhovens 2009 109 256 69 253 7.1% 1.56 [1.22, 2.00]
Subtotal (95% CI) 960 701 22.2% 2.57 [1.44, 4.59]
Total events 246 95
Heterogeneity: Tau² = 0.23; Chi² = 11.92, df = 3 (P = 0.008); I² = 75%
Test for overall effect: Z = 3.18 (P = 0.001)
5.3.2 adalimumab 40 mg 2 hetente
Furst STAR 2003 47 318 11 318 5.8% 4.27 [2.26, 8.09]
Keystone 2004 43 207 5 200 4.8% 8.31 [3.36, 20.55]
Kim 2007 13 65 4 63 4.2% 3.15 [1.09, 9.14]
Weinblatt 2003 ARMADA 18 67 3 62 3.9% 5.55 [1.72, 17.93]
Subtotal (95% CI) 657 643 18.8% 4.91 [3.18, 7.58]
Total events 121 23
Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 3 (P = 0.53); I² = 0%
Test for overall effect: Z = 7.17 (P < 0.00001)
5.3.3 certolizumab 200mg
Keystone 2008 RAPID1 84 393 6 199 5.2% 7.09 [3.15, 15.94]
Smolen 2009 RAPID2 39 246 1 127 2.1% 20.13 [2.80, 144.86]
Subtotal (95% CI) 639 326 7.3% 8.24 [3.89, 17.44]
Total events 123 7
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 5.51 (P < 0.00001)
5.3.4 etanercept 2x25 mg hetente
Weinblatt 1999 9 59 0 30 1.2% 9.82 [0.59, 163.15]
Subtotal (95% CI) 59 30 1.2% 9.82 [0.59, 163.15]
Total events 9 0
Heterogeneity: Not applicable
Test for overall effect: Z = 1.59 (P = 0.11)
5.3.5 golimumab 50mg
Keystone 2008 GO-FORWARD 18 89 7 133 5.1% 3.84 [1.67, 8.82]
Kremer 2010 8 129 4 129 3.9% 2.00 [0.62, 6.48]
Subtotal (95% CI) 218 262 9.0% 3.09 [1.57, 6.09]
Total events 26 11
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 3.26 (P = 0.001)
5.3.6 infliximab 3 mg/kg 8 hetente
Maini 1999 ATTRACT 7 86 0 88 1.2% 15.34 [0.89, 264.59]
Schiff 2008 ATTEST 40 165 10 110 5.8% 2.67 [1.39, 5.11]
Westhovens 2006 48 360 16 363 6.2% 3.02 [1.75, 5.23]
Subtotal (95% CI) 611 561 13.2% 2.97 [1.97, 4.50]
Total events 95 26
Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 5.16 (P < 0.00001)
5.3.7 rituximab 2x1000mg
Edwards 2004 9 40 2 40 3.1% 4.50 [1.04, 19.54]
Emery 2006 DANCER 24 192 6 149 5.0% 3.10 [1.30, 7.40]
Emery 2010 SERRENE 17 172 9 172 5.3% 1.89 [0.87, 4.12]
Subtotal (95% CI) 404 361 13.3% 2.57 [1.50, 4.41]
Total events 50 17
Heterogeneity: Tau² = 0.00; Chi² = 1.35, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 3.43 (P = 0.0006)
5.3.8 tocilizumab 8mg
Genovese 2008 TOWARD 169 805 12 415 6.1% 7.26 [4.09, 12.88]
Smolen OPTION 2008 45 205 4 204 4.5% 11.20 [4.10, 30.56]
Yazici 2012 ROSE 73 409 4 207 4.5% 9.24 [3.42, 24.92]
Subtotal (95% CI) 1419 826 15.1% 8.30 [5.32, 12.95]
Total events 287 20
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 9.32 (P < 0.00001)
Total (95% CI) 4967 3710 100.0% 4.19 [2.99, 5.85]
Total events 957 199
Heterogeneity: Tau² = 0.40; Chi² = 80.32, df = 21 (P < 0.00001); I² = 74%
Test for overall effect: Z = 8.36 (P < 0.00001)
Test for subgroup differences: Chi² = 22.30, df = 7 (P = 0.002), I² = 68.6%
0.01 0.1 1 10 100
Favours placebo Favours biologics

8.7 Literature search strategies for cost-utility articles

Ovid MEDLINE(R) 1946 to Present with Daily Update, 23rd April, 2012
Search strategy (number of hits):

1	Arthritis, Rheumatoid/	(76115)
2	(rheum$ adj (arthrit$ or arthropath$)).ti,ab.	(67563)
3	1 or 2	(93337)
4	(etanercept or enbrel or tnfr-fc).ti,ab,rn.	(4169)
5	(infliximab or remicade).ti,ab,rn.	(6777)
6	(adalimumab or humira or D2E7).ti,ab,rn.	(2281)
7	(golimumab or simponi).ti,ab,rn.	(144)
8	(tocilizumab or roactemra or ro-actemra).ti,ab,rn.	(417)
9	(certolizumab or certolizumab pegol or cimzia).ti,ab,rn.	(286)
10	(rituximab or mabthera).ti,ab,rn.	(8305)
11	(abatacept or orencia).ti,ab,rn.	(2102)
12	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	(20282)
13	3 and 12	(4211)
14	economics/	(26255)
15	exp "Costs and Cost Analysis"/	(163753)
16	VALUE OF LIFE/	(5209)
17	economics, dental/	(1837)
18	exp economics, hospital/	(17845)
19	economics, medical/	(8438)
20	economics, nursing/	(3860)
21	economics, pharmaceutical/	(2316)
22	(econom$or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom$).ti,ab.	(129853)
23	(expenditure$ not energy).ti,ab.	(14949)
24	(value adj1 money).ti,ab.	(18)
25	budget$.ti,ab.	(15206)
26	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	(301032)
27	((energy or oxygen) adj cost).ti,ab.	(2405)
28	(metabolic adj cost).ti,ab.	(635)
29	((energy or oxygen) adj expenditure).ti,ab.	(13888)
30	27 or 28 or 29	(16292)
31	26 not 30	(300287)
32	letter.pt.	(743838)
33	editorial.pt.	(296310)
34	historical article.pt.	(281817)
35	32 or 33 or 34	(1308587)
36	31 not 35	(278751)
37	Animals/	(4916135)
38	Humans/	(12224012)
39	37 not (37 and 38) [Including Related Terms]	(17936)
40	36 not 39	(278456)
41	13 and 40	(196)
42	limit 41 to yr="2008 -Current"	**(85)**

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <, 23rd April, 2012>
Search Strategy (number of hits):

1	(rheum$ adj (arthrit$ or arthropath$)).ti,ab.	(2856)
2	(etanercept or enbrel or tnfr-fc).ti,ab,rn.	(267)
3	(infliximab or remicade).ti,ab,rn.	(462)
4	(adalimumab or humira or D2E7).ti,ab,rn.	(219)
5	(golimumab or simponi).ti,ab,rn.	(20)
6	(tocilizumab or roactemra or ro-actemra).ti,ab,rn.	(76)
7	(certolizumab or certolizumab pegol or cimzia).ti,ab,rn.	(36)
8	(rituximab or mabthera).ti,ab,rn.	(645)
9	(abatacept or orencia).ti,ab,rn.	(36)
10	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	(1439)
11	1 and 10	(314)

12	(econom$or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom$).ti,ab.	(8466)
13	(expenditure$ not energy).ti,ab.	(733)
14	(value adj1 money).ti,ab.	(2)
15	budget$.ti,ab.	(1456)
16	12 or 13 or 14 or 15	(10213)
17	11 and 16	**(15)**

Web of knowledge, http://apps.webofknowledge.com, 23 rd April, 2012
Number of hits and search strategy:
7 **250**
#5 NOT #6 Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=2008-2012 Lemmatization=On
# 6 553,255
TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovin or sheep or guinea*) Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=2008-2012 Lemmatization=On
# 5 253
#4 AND #3 Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=2008-2012 Lemmatization=On
# 4 420,694
TS=(econom* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom* or budget*) Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=2008-2012 Lemmatization=On
# 3 4,049
#2 AND #1 Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=2008-2012 Lemmatization=On
# 2 15,363
TS=(etanercept or enbrel tnfr-fc or infliximab or remicade or adalimumab or humira or D2E7 or golimumab or simponi or tocilizumab or roactemra or ro-actemra or certolizumab or certolizumab pegol or cimzia or rituximab or mabthera or abatacept or orencia) Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=2008-2012
Lemmatization=On
# 1 27,503
TS=((rheum* same arthrit*) or (rheum* same arthropath*)) Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=2008-2012 Lemmatization=On

Search http://www.crd.york.ac.uk/CRDWeb, 23rd April, 2012.
Search strategy and number of hits:

1	MeSH DESCRIPTOR Arthritis, Rheumatoid EXPLODE ALL TREES	400
2	(((rheum* NEAR arthrit*))) WHERE PD FROM 22/09/2008 TO 23/04/2012	368
3	#1 OR #2	580
4	((etanercept OR enbrel OR infliximab OR remicade OR adalimumab OR humira OR D2E7 or tocilizumab OR roactemra OR ro-actemra OR certolizumab OR certolizumab pegol OR cimzia OR rituximab OR mabthera OR abatacept OR orencia)) WHERE PD FROM 22/09/2008 TO 23/04/2012	255
5	#3 AND #4	100

8.8 Results of the health economic literature search (references and abstracts)

See webpage: http://hecon.uni-corvinus.hu

Péntek (ed.): Biologicals in Rheumatoid Arthritis – Appendix 8.8