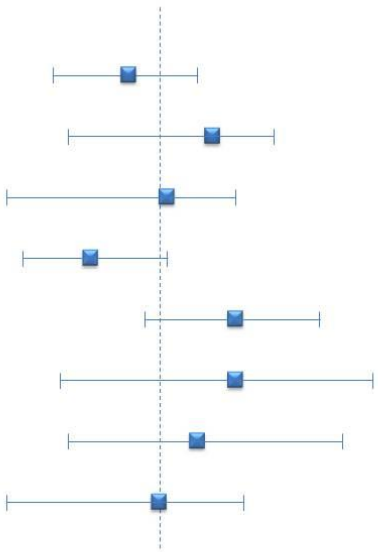
Systematic review and analysis of evidences on clinical efficacy and cost-effectiveness of biological drugs for the treatment of Ankylosing Spondylitis



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2 List of abbreviations

AE	Adverse Event
AS	Ankylosing Spondylitis
ASAS	Assessment in SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
CI	Confidence Interval
CD	Chron's Disease
DMARD	Disease Modifying Anti-Rheumatic Drugs
EOW	Every Other Week
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
MASES	Maastricht Ankylosing Spondylitis Enthesis Score
MCMC	Markov Chain Monte Carlo
MTC	Mixed Treatment Comparison
MTX	Methotrexate
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NRS	Numerical Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
RCT	Randomized Controlled Trial
RD	Risk Difference
RR	Relative Risk
TNF	Tumour Necrosis Factor
VAS	Visual Analogue Scale

3 Summary

Technology: Infliximab and comparator biological such as adalimumab, etanercept, golimumab.

Conditions: Ankylosing spondylitis (AS)

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

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

Results: Clinical efficacy of biological therapies is based on good clinical evidences regarding to all clinical efficacy endpoints (ASAS20, ASAS40, ASAS 5/6, and BASDAI 50% response). Altogether, 22 trials are included in our meta-analysis, 12 infliximab, 3 adalimumab studies, 6 etanercept and 1 golimumab. Efficacy of biological treatments for the treatment of AS has been established by clinical scientific evidences, significant improvement at all outcomes considered was confirmed. According to the results of indirect comparison, there were no significant difference between biological treatments and placebo in terms of safety and tolerability endpoints. We found no significant difference between the clinical efficacy and safety of infliximab, adalimumab, etanercept and golimumab therapies. Cost-utility analysis of adalimumab and/or infliximab, etanercept and golimumab treatment for AS were performed in the UK, Canada, The Netherlands, Germany, Spain and France. There are no cost-utility studies from Eastern Central Europe.

Implications for decision making: Efficacy of infliximab and comparator biologicals for the treatment of Ankylosing Spondylitis (AS) was proved by clinical evidence, significant improvement at all outcomes considered was confirmed. We found no significant differences in efficacy and safety of different biological treatments. Health economics results suggest that biological therapies are cost-effective alternatives for the treatment of AS in group of developed high income countries. There is a lack of health economics results in Central-Eastern European countries however these data are more and more required by governments and funders as part of the company economic dossiers.

4 Background

4.1 Description of the health problem

Spondyloarthritis (SpA) represents a group of interrelated diseases (ankylosing spondylitis - AS, psoriatic arthritis - PsA, arthritis/spondylitis with inflammatory bowel disease, reactive arthritis) with common clinical features and a close association with a specific genetic predisposition presented by the human leukocyte antigen-27 (HLA-B27). Patients with SpA can be distinguished according to their clinical presentation as patients with predominantly axial SpA or with predominantly peripheral SpA.

Ankylosing spondylitis (AS), the prototype disease in the spectrum of spondyloarthritides (SpA), is a chronic disabling inflammatory disorder, generally starting early in life. Inflammatory back pain due to sacroiliitis and spondylitis, and formation of syndesmophytes leading to ankylosis of the spine, characterize AS, but the disease may involve also peripheral joints, eye, gut and aorta.[56] The most common extra-articular manifestations in AS are represented by uveitis, inflammatory bowel disease, heart, lung, skin, bone and kidney involvement.[19]

Back pain is the leading clinical symptom, which presents typically as inflammatory back pain that is characterized by morning stiffness and improvement by exercise. In 90% or more cases, the disease starts with a sacroiliitis. Further in the course of the disease, the whole spine can be affected with spondylitis, spondylodiscitis, and arthritis of the small intervetebral joints, however, not all AS patients have or develop syndesmophytes. Even in patients with longer-standing disease, syndesmophytes are present in only about 50% of cases and only a smaller percentage of these patients develop the typical clinical picture of patients with an ankylosed spine, where the name AS comes from. The term AS was introduced around 1900 at a time when a diagnosis could be made only on the basis of the clinical experience, without the help of imaging or laboratory results. It has been suggested that the term axial SpA, covering patients early in the course of the disease and patients with a less progressive course, seems to be more adequate, whereas the term AS should be reserved for the more advanced 'ankylosed' phase of the disease.[53]

The mystifying significant male predominance among patients with AS began to abate several decades ago along with studies demonstrating a 2–3:1 male-to-female ratio rather than the previously thought 5–6:1.[56] Very recent studies on patients with axial SpA, which did not show any gender difference in disease prevalence, raised the possibility that female patients may have some atypical disease manifestations, with inflammatory back pain being less frequent on presentation and enthesopathy and generalized pain syndrome heading the clinical picture, as well as slower development of typical radiographic changes of AS, as compared to males.

Patients with AS suffer from an increased cardiovascular (CV) risk. It appears to be a clear contribution of the "traditional" CV risk factors, as well as the underlying chronic inflammatory process, to the increased atherosclerotic risk in AS.[45, 48]

Ankylosing spondylitis can have important socioeconomic consequences for individual patients and for society. Employment rates for AS patients are significantly decreased in men, but not in women when compared to the general population. AS-related sick leave in patients in paid work varies between 6.5 and 18 days per patient per year and between 15% and 20% of AS patients require help from relatives or friends to complete unpaid tasks.[6] Cost-of-illness studies are available from Brazil, Germany, Hong Kong, Sweden, Spain, Tunisia, The Netherlands, Brazil UK and US. The studies that analyse direct and indirect costs report very different values but all agree on the fact that the societal impact of AS is mainly related to indirect cost (loss of productivity). The most important predictor for high costs both in the first and in the fifth year of the disease is functional disability.[47] In the Czech Republic data from two cross sectional studies (Beda I, 2005, n=1008; Beda II, 2008, n=509) were analysed, mean age of the samples were 50.2 and 52.5 years, respectively and the disease duration was 23.0 and 26.4 years. Mean total annual costs per patient in the sample were €4,782 in Beda I and €5,806 in Beda II, the average direct costs per patient in the sample per year are estimated at €1,812 (Beda I) and €2,588 (Beda II) The largest direct cost burdens were spa procedures (45.3 %, Beda I) and biological drugs (52.8 %, Beda II).[49]

4.2 Classification criteria

4.2.1 Modified New York criteria (1984) for diagnosis of ankylosing spondylitis (AS)

A definite diagnosis of AS requires the radiological criterion and at least one clinical criterion to be satisfied as defined below[64]:

Radiological criterion:
Sacroiliitis at least grade 2 bilaterally or grade 3 or 4 unilaterally.

Clinical criteria:

- Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest.
- Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
- Limitation of chest expansion relative to normal values correlated for age and sex.

All reasonable measures should be taken to ensure that symptoms are due predominantly to AS and that alternative causes, including spinal fracture, disc disease and fibromyalgia, are excluded.

4.2.2 ASAS classification criteria for axial spondyloarthritis (SpA)

The established classification criteria (New York criteria and lately the modified New York criteria) for AS date back over 20 years and rely on the combination of clinical symptoms plus unequivocal radiographic sacroiliitis of at least grade 2 bilaterally or grade 3 unilaterally. However, the radiographs are often normal when symptoms arise and it usually takes several years for definite radiographic sacroiliitis to evolve. The most recent Assessment in SpondyloArthritis international Society (ASAS) classification criteria for axial spondyloarthritis (SpA) were developed for early and established cases and include the

magnetic resonance imaging (MRI) technique (active inflammation) and HLA-B27 as an important tool for early diagnosis.

ASAS classification criteria for axial SpA covering patients with non-radiographic and radiographic axial SpA[52]:

I. In patients with ≥3 months back pain (with/without peripheral manifestation) and age onset <45 years: sacroiliitis on imaging plus ≥1 SpA feature OR HLA-B27 plus ≥2 other SpA features (SpA features are: inflammatory back pain (IBP), arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn‘s/ ulcerative colitis, good response to NSAIDs, family history for SpA, HLA-B27, elevated CRP)

II. In patients with peripheral manifestations only: arthritis or enthesitis or dactylitis plus a.) ≥1 SpA feature (uveitis, psoriasis, Crohn‘s/ulcerative colitis, preceding infection, HLA-B27, sacroiliitis on imaging) OR b.) ≥2 other SpA features (arthritis, enthesitis, dactylitis, IBP ever, family history for SpA)

4.3 Epidemiology of AS

The incidence and prevalence of AS has been studied in various populations. The incidence was shown to be relatively stable in northern Norway over 34 years at 7.26 per 100,000. Prevalence varied from 0.036% to 0.10%. In Greece and Japan, the incidence and prevalence of AS were significantly lower. The incidence mirrors the prevalence of HLA-B27 seropositivity.[21]

4.4 Health status assessment in AS

The Assessment in SpondyloArthritis international Society (ASAS) provides a comprehensive handbook on the most relevant aspects for the assessments of spondyloarthritis (SpA), including AS.[54]

4.4.1 Disease activity: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The purpose of this tool is to measure patient-reported disease activity in patients with AS. The instrument was first published in 1994 using visual analogue scales. The index includes patient-reported levels of back pain, fatigue, peripheral joint pain and swelling, localized tenderness, and the duration and severity of morning stiffness. Consist of 6 items, the response options/scale are numeric response scales (0–10) or visual analogue scales (VAS, 0–10 cm) anchored by adjectival descriptors "none" and "very severe." Duration of morning stiffness is anchored by a time scale (0–2 or more hours). The BASDAI has been endorsed by the Assessment of SpondyloArthritis international Society (ASAS) for the measurement of disease activity. The BASDAI has been the most frequently used measure of disease activity in clinical trials and is recommended to assess response to anti-tumour necrosis factor therapies in AS patients. It is available online (in multiple translations) at http://www.asas-group.org. For scoring, the scores for questions 5 and 6 (severity and duration of morning stiffness) are averaged, the result is then averaged with the remaining 4 question scores to give a final score out of 10. BASDAI ranges from 0 (no disease activity) to 10 (maximal disease activity). A cut off of 4 is used to define active disease.[65]

4.4.2 Disease activity: Ankylosing Spondylitis Disease Activity Score (ASDAS)

To measure disease activity in ankylosing spondylitis (AS) based on a composite score of domains relevant to patients and clinicians, including both self reported items and objective measures.

Parameters used for the ASDAS are.

1) Total back pain (BASDAI question 2)

2) Patient global of disease activity (How active was your spondylitis on average during the last week? Response: Visual Analogue Scale – VAS; 0-10 Numerical Rating Scale - NRS)

3) Peripheral pain/swelling (BASDAI question 3)

4) Duration of morning stiffness (BASDAI question 6)

5) C-reactive protein (CRP) in mg/litre (or erythrocyte sedimentation rate (ESR)).

Calculation of ASDAS

ASDAS(CRP): 0.121xtotal back pain+0.110xpatient global+0.073xperipheral pain/swelling+0.058xduration of morning stiffness+0.579xLn(CRP+1).

ASDAS(ESR): 0.113xpatient global+0.293x√ESR+0.086xperipheral pain/swelling+0.069xduration of morning stiffness+0.079xtotal back pain.

ASDAS(CRP) is preferred, but the ASDAS(ESR) can be used in case CRP data are not available. (CRP in mg/litre; all patient assessments on a 10 cm scale.)

The ASDAS and aids for its calculation are available online at http://www.asas-group.org. The ASDAS was sensitive to improvement with TNF inhibitors in patients with axial spondylarthritis. The ASAS group defined 4 important disease states by consensus: inactive disease, moderate, high, and very high disease activity, and relevant cut offs between these states were calculated from the NOR-DMARD database at 1.3, 2.1, and 3.5 units, respectively. Clinically important improvement was found to be 1.1 units or greater and major improvement was defined as a change of 2.0 units or more.

4.4.3 Functional status: Bath Ankylosing Spondylitis Functional Index (BASFI)

BASFI was developed in 1994 to define and monitor physical functioning in patients with AS. Eight items concerning activities referring to the functional anatomy of the patients (bending, reaching, changing position, standing, turning, and climbing steps), and 2 items assessing the patients' ability to cope with everyday life. The questionnaire consists of 10 items, responses are given on numeric response scales (0–10) or visual analogue scale (0–10 cm) anchored by adjectival descriptors "easy" and "impossible." BASFI is endorsed by the Assessment of SpondyloArthritis international Society. The BASFI is the most widely used functional index for assessment of AS patients, primarily in studies of disease impact and in clinical trials. BASFI is available online at http://www.asasgroup.org. Scoring: the mean of the individual scores is calculated to give the overall index score. Score range is 0–10, with 0 reflecting no functional impairments and 10 reflecting maximal impairment.[65]

4.4.4 Bath Ankylosing Spondylitis Metrology Index (BASMI)

BASMI dates back to 1994 and it was developed to quantify the mobility of the axial skeleton in AS patients and allow objective assessment of clinically significant changes in spinal movement. Clinical measures of cervical rotation, tragus to wall distance, lumbar flexion, lumbar side flexion, and intermalleolar distance. The tool consist of 5 items, each item is scored from 0–10 based on individually defined cut points. Ranges are given as cervical rotation (>85.0° to ≤8.5°), tragus to wall (>10 cm to ≤38 cm), lumbar flexion (>7.0 cm to ≤0.7 cm), lumbar side flexion (>20.0 cm to ≤1.2 cm), and intermalleolar distance (>120 cm to ≤30 cm). BASMI is endorsed by the Assessment of SpondyloArthritis international Society (ASAS).

The BASMI is included in the ASAS core sets as the preferred measure of spinal mobility. It has been used in clinical trials of anti–tumour necrosis factor agents in AS patients, and more recently was the outcome measure used to show that spinal mobility is determined by both spinal inflammation and by structural damage. The BASMI10 is available at http://www.asif.rheumanet.org/basmi-10-e.pdf, and the linear version is available at http://www.asif.rheumanet.org/basmi-lin-e.pdf. Measurements are performed by health care providers who have been trained to perform the clinical examinations required. In the original instrument, each continuous assessment was converted into a nominal score of 0, 1, or 2. The next year a second nominal version was published, with individual assessments scored between 0 and 10. More recently a linear version has been proposed (BASMI-lin), with scoring ranges similar to the second nominal version. Individual scores are summed for the BASMI-original or averaged for the second nominal BASMI to give a final score between 0 and 10, where a higher score reflects more significant impairment of spinal mobility. Normative values have been published.

4.4.5 Assessment of treatment response

4.4.5.1 ASAS 20 / 40 improvement criteria

ASAS 20 improvement:

- Four domains:

  – Patient global (How active was your spondylitis on average during the last week? Visual Analogue Scale – VAS; 0-10 Numerical Rating Scale - NRS)

  – Pain (Two questions on average last week, VAS or NRS: – How much pain of your spine due to AS do you have? How much pain of your spine due to AS do you have at night?)

  – Function (BASFI)

  – Inflammation (mean of BASDAI questions 5 and 6).
- Improvement of >20% and >1 unit in at least 3 domains on a scale of 10.
- No worsening of >20% and >1 unit in remaining domain on a scale of 10.

ASAS 40 improvement:

- Four domains:

  – Patient global (How active was your spondylitis on average during the last week? (Visual Analogue Scale – VAS; 0-10 Numerical Rating Scale - NRS)

  – Pain (Two questions on average last week, VAS or NRS: – How much pain of your spine due to AS do you have? How much pain of your spine due to AS do you have at night?)

  – Function (BASFI)

  – Inflammation (mean of BASDAI questions 5 and 6).
- Improvement of >40% and >2 unit in at least 3 domains on a scale of 10.
- No worsening at all in remaining domain.

ASAS 5/6 criteria

- Six domains:

  – Patient global (How active was your spondylitis on average during the last week? (Visual Analogue Scale – VAS; 0-10 Numerical Rating Scale - NRS)

– Pain (Two questions on average last week, VAS or NRS: – How much pain of your spine due to AS do you have? How much pain of your spine due to AS do you have at night?)

– Function (BASFI)

– Inflammation (mean of BASDAI questions 5 and 6)

– CRP

– Spinal mobility (see: ASAS core set)

- Improvement of >20% in at least five domains.

ASAS partial remission criteria

- Four domains:

  – Patient global (see Box 26)

  – Pain (see Box 25)

  – Function (see Box 29)

  – Inflammation (mean of BASDAI questions 5 and 6).

- A value not above 2 units in each of the domains on a scale of 10.

4.4.5.2 ASDAS improvement

See section 4.4.2.

4.4.6 ASAS core set for disease-controlling antirheumatic treatments

The core set covers the following domains and instruments to be used for the assessment are also listed[54]:

Domain	Instrument
Function	BASFI
Pain	Numerical rating scale 0-10 (NRS)/VAS (last week/spine/at night due to AS)
	NRS/VAS (last week/spine/due to AS)
Spinal mobility	Chest expansion
	Modified Schober
	Occiput to wall
	Cervical rotation
	lateral spinal flexion or BASMI
Patient global	NRS/VAS (global disease activity last week)
Peripheral joints and entheses	Number of swollen joints (44-joint count)
	Validated enthesitis scores, such as MASES, San Francisco and Berlin
x Ray spine	Lateral lumbar spine and lateral cervical spine
Stiffness	NRS/VAS (duration of morning stiffness/spine/last week)
Acute phase reactants	C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)
Fatigue	Fatigue question BASDAI

4.5 Management of AS

The ASAS/EULAR recommendations for the treatment of AS were updated in 2010. The recommendations were formulated for patients fulfilling the modified New York criteria for AS, independent of extra-articular manifestations.[12]

The recommendations are as follows:

The overarching principles of the management of patients with AS are:

AS is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary treatment coordinated by the rheumatologist.

- The primary goal of treating the patient with AS is to maximise long term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalisation of function and social participation.
- Treatment of AS should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.
- The optimal management of patients with AS requires a combination of non-pharmacological and pharmacological treatment modalities.
-

1. General treatment

The treatment of patients with AS should be tailored according to:

- The current manifestations of the disease (axial, peripheral, entheseal, extra-articular symptoms and signs).
- The level of current symptoms, clinical findings, and prognostic indicators.
- The general clinical status (age, gender, comorbidity, concomitant medications, psychosocial factors).

2. Disease monitoring

The disease monitoring of patients with AS should include:

- Patient history (eg, questionnaires)
- Clinical parameters
- Laboratory tests
- Imaging
- All according to the clinical presentation as well as the ASAS core set

The frequency of monitoring should be decided on an individual basis depending on:

- Course of symptoms
- Severity
- Treatment

3. Non-pharmacological treatment

- The cornerstone of non-pharmacological treatment of patients with AS is patient education and regular exercise.
- Home exercises are effective. Physical therapy with supervised exercises, land or water based, individually or in a group, should be preferred as these are more effective than home exercises.
- Patient associations and self-help groups may be useful.

4. Extra-articular manifestations and comorbidities

- The frequently observed extra-articular manifestations, for example, psoriasis, uveitis and IBD, should be managed in collaboration with the respective specialists.
- Rheumatologists should be aware of the increased risk of cardiovascular disease and osteoporosis.

5. Non-steroidal anti-inflammatory drugs

- NSAID, including Coxibs, are recommended as first-line drug treatment for AS patients with pain and stiffness.
- Continuous treatment with NSAID is preferred for patients with persistently active, symptomatic disease.
- Cardiovascular, gastrointestinal and renal risks should be taken into account when prescribing NSAID.

6. Analgesics

- Analgesics, such as paracetamol and opioid (like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated.

7. Glucocorticoids

- Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered.
- The use of systemic glucocorticoids for axial disease is not supported by evidence.

8. Disease-modifying antirheumatic drugs

- There is no evidence for the efficacy of DMARD, including sulfasalazine and methotrexate, for the treatment of axial disease.
- Sulfasalazine may be considered in patients with peripheral arthritis.

9. Anti-TNF therapy

- Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations.
- There is no evidence to support the obligatory use of DMARD before or concomitant with anti-TNF therapy in patients with axial disease.
- There is no evidence to support a difference in efficacy of the various TNF inhibitors on the axial and articular/entheseal disease manifestations; but in the presence of IBD a difference in gastrointestinal efficacy needs to be taken into account.
- Switching to a second TNF blocker might be beneficial especially in patients with loss of response.
- There is no evidence to support the use of biological agents other than TNF inhibitors in AS.

10. Surgery

- Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age.
- Spinal corrective osteotomy may be considered in patients with severe disabling deformity.
- In patients with AS and an acute vertebral fracture a spinal surgeon should be consulted.

11. Changes in the disease course

- If a significant change in the course of the disease occurs, other causes than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed.

A recent update on the role of non-biological therapies in AS confirmed that physical therapy in various modalities has positive effects on pain and function in AS. Non-steroidal

antiinflamatory drugs (NSAIDs) including coxibs improve standard outcomes (BASDAI, BASFI) and disease activity in AS. Disease modifying antirheumatic drugs (DMARDs) have no effects on BASDAI, BASFI and pain in AS.[59] An update on the treatment of AS with biologicals stated that all recent literature data support the use of the currently available TNF blockers in AS. Data from first studies of patients with nonradiographic SpA show a similar response to TNF blockers. There was no change in the incidence of adverse events during anti-TNF treatment in SpA.[2]

5 Clinical efficacy and safety of biological medications of ankylosing spondylitis

Summary

Direct and indirect meta-analyses of data from randomized controlled trials identified by systematic literature search were conducted to demonstrate the efficacy and safety of infliximab, adalimumab, etanercept, golimumab in ankylosing spondylitis. Biological therapies were superior to placebo treatment in terms of all efficacy endpoints examined in this study (ASAS20, ASAS40, ASAS 5/6, and BASDAI 50% response). No significant differences were found between safety and tolerability of biological treatments (infliximab, adalimumab, etanercept, golimumab) and placebo in terms of adverse event, serious adverse events, adverse events leading to the discontinuation of the therapy, infection, and serious infection. According the results of indirect comparison, we found no significant differences between the efficacy and safety of different biologic treatments either.

5.1 Objectives

The main aims of this systematic review were:

1. to identify all clinical efficacy and safety evidence for infliximab and comparator biological drugs for the treatment of ankylosing spondylitis (AS)
2. to conduct an up-to-date meta-analysis on efficacy and safety outcomes
3. to generate an overview of recently published systematic reviews.

Methods used in this analysis were strongly corresponding to NICE Decision Support Unit's recommendations about the evidence synthesis and to Cochrane Handbook's recommendations.[25]

5.2 Methods

5.2.1 Comparators

In this analysis, adalimumab, etanercept and golimumab are considered as comparators for infliximab.

The doses included in the analysis are as follows:

1. Adalimumab: 40 mg every other week
2. Etanercept: 25 mg twice weekly, or 50 mg once weekly
3. Golimumab: 50 mg once a month
4. Infliximab: 5 mg/kg at 0, 2, 6 weeks and then every 6 to 8 weeks

5.2.2 Search strategies

Electronic databases (Medline and Cochrane Library) as well as references of retrieved articles were searched.

In 2007 McLeod et al. published a review, which assesses the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis (AS). Their research strategy covers the RCTs published till November, 2005. Until this date we used the list of the RCTs identified by McLeod 2007. After this date, the Cochrane Highly Sensitive Search Strategy[25] was applied to identify randomized controlled publications and was combined with the disease name (ankylosing spondylitis, ankylosing spondyloarthritis, spondyloarthritide – as well as their combinations) and drug names (infliximab, adalimumab, etanercept, golimumab). Meta-analyses were identified by applying the relevant publication type limit. Exact search terms are presented in Appendix 0. The search dates were 1st November 2005, the end date of the search: 15th March 2013.

5.2.3 Inclusion and exclusion criteria

5.2.3.1 Inclusion criteria

- Randomized controlled trials 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 adalimumab, etanercept, golimumab or infliximab treatment.
- The patients of interest are adults with AS.

5.2.3.2 Exclusion criteria

- Non randomized or uncontrolled studies, observational studies, case series, letters to editor, studies with no abstracts or with conference abstracts only.
- Trials in diseases other than AS.
- Off-label doses.
- Studies reporting solely on laboratory measures aimed at investigating disease, or treatment mechanisms and which do not report relevant clinical outcomes.
- Studies on patients with age <18.
- Pilot studies.
- Studies, where study duration is <12 weeks.

5.2.4 Data abstraction

Data were extracted by two independent researchers 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
- Trial Duration (weeks)
- Treatment
- Comparator

We evaluate the following efficacy endpoints:

Clinical Efficacy Measures

- ASAS20
- ASAS40
- ASAS5/6
- ASAS partial remission
- BASDAI 50% response

ASAS20: 20% improvement response according to the criteria of the ASsessment in Ankylosing Spondylitis (ASAS) International Working Group: at least 20% improvement from baseline and had an absolute improvement from baseline of at least 1 unit (on a scale of 0–10) in at least 3 of the following 4 assessment domains: patient's global assessment, spinal pain, function according to the Bath Ankylosing Spondylitis Functional Index (BASFI), and morning stiffness (the average of the last 2 questions of the BASDAI). In addition, ASAS20 responders must not have had deterioration from baseline (defined as a worsening of ≥20% and an absolute worsening of at least 1 unit (on a scale of 0–10) in the potential remaining assessment domain.

ASAS40 response: 40% improvement from baseline and an absolute improvement of at least 2 units [on a scale of 0–10] in at least 3 of the 4 assessment domains defined in the ASAS20 response criteria, with no deterioration from baseline in the potential remaining assessment domain), ASAS partial remission (an absolute score of≥2 in each of the above 4 ASAS assessment domains)

ASAS5/6: 20% improvement in at least 5 of the following 6 ASAS assessment domains: spinal pain, patient's global assessment, function according to the Bath Ankylosing Spondylitis Functional Index (BASFI), morning stiffness, CRP level, and the Bath Ankylosing Spondylitis Metrology Index (BASMI) score.
ASAS partial remission: a value of 2 on a 0–10 scale in each of the 4 domains of the ASAS20.

BASDAI 50: the proportion of patients who had at least 50% improvement in the BASDAI score.

We distinguish between study endpoints measured at week 12 and 24.

We also evaluate tolerability and safety of biological therapies.

Tolerability Measures

- Adverse events leading to discontinuation of therapy

Safety Measures

- Adverse events
- Serious adverse events
- Infections
- Serious infections
- Injection-site reaction

5.2.5 Quality assessment

The quality of selected studies was evaluated using the Jadad-score.[32] This is the most frequently used scale in quality assessment of clinical trials.[46] 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.

5.2.6 Comparison

5.2.6.1 Meta-analysis

We have conducted a meta-analysis to compare the efficacy and safety of the biologicals included in the study.

Two specific analyses were proceeded for this meta-analysis:

1. direct comparison: a frequentist meta-analysis of study outcomes for biological therapies with adalimumab, etanercept, golimumab and infliximab.
2. an indirect comparison for therapies with adalimumab, etanercept, golimumab and infliximab.

5.2.6.2 Direct comparison

Data were analysed using Review Manager 5 software. The Relative Risk (RR) and 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 when analyzing efficacy since no significant heterogeneity was detected in the studies, and CI were calculated using random effect model when examining safety, since significant heterogeneity was identified in relevant number of the cases. The chi-square test for heterogeneity was computed with a P-value set to 0.10 to determine statistical significance.

5.2.6.3 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.

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 significantly significant at the 0.05 level if the 95% CIs around the odds ratio did not cross.

The probability of being the best treatment is also reported in the efficacy endpoints for each biological.

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

5.2.6.4 Presentation of results

We give a detailed description of the included trials identified in the literature and also about the quality assessment of each trial. Outcomes of all included RCT trials will be analyzed and combined in one meta-analysis. Detailed description 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 presented separately since it includes indirect comparisons of biologics. Results will be presented by outcome (e.g., ASAS20, ASAS40, ASAS5/6, ASAS partial remission, BASDAI 50% response, adverse events, serious adverse events, adverse events leading to the discontinuation of therapy, infections and injection-site reactions).

5.3 Results: meta-analysis of randomized controlled trials

5.3.1 Included studies

5.3.1.1 Results of the search strategy for the period 2005-2013

Our search strategy for the period 1st November 2005 – 15th March 2013 identified 313 items (see Appendix 8.2).
In the first round we excluded non-RCTs, RCTs in other disease (e.g. psoriasis), papers which were duplications of RCTs or presented post-hoc analysis of previous RCT results, open-label trials and open label extensions of RCT-s.

Eighteen studies were identified which met the inclusion criteria (see

Table 1). In the text we refer to the studies by indicating the first author and the year of publication. Out of the 18 studies, one study was excluded because it examined low-dose (3 mg/kg - off-label dose) infliximab therapy[31], one study examined high dose of etanercept[43].

We excluded one study, which examined a narrower study population, patients with HLA B27[3], and two studies, which examined patients with non-radiographic axial spondyloarthritis[24, 55].[i] Two studies were excluded as infliximab therapy was presented in both treatment arms (infliximab+MTX vs infliximab).[37, 40] Braun 2011[13] was excluded as this study examined the efficacy of etanercept versus sulfasalazine.[ii] Breban 2008[14] was excluded as it examined infliximab therapy on demand. Hu 2012[26] was excluded as this study examined other end-points than examined in this study. Huang 2010[27] was excluded because it was a 6 weeks trial. Cantini 2013[16] was a long-term follow up study of patients in remission.

These studies were not included in the meta-analysis however, we present the study design and results of infliximab studies in the next chapter.

[i] Axial spondyloarthritis (SpA) may be split into two categories: 1) ankylosing spondylitis (AS) (examined in this study) and 2) nonradiographic axial spondyloarthritis (nr-axSpA) by the 1984 modified New York criteria which require the presence of sacroiliitis on plain x-ray for the classification of AS
[ii] Theoretically these three studies could have been included in the mixed treatment comparison, if we had identified a study were one treatment arm (comparator) was the same and had been compared to an othe biologs (e.g. study 1: etanercept vs sulfasalazine and study 2: sulfasalazine vs biologic other than etanercept.

We included five studies identified after November 2005 in the meta-analysis: one adalimumab study[28], three etanercept studies[4, 18, 62] and one golimumab study[30].

Table 1 Identified studies 2005-2013 (search after November, 2005)

References	Drug	Excl./Incl.
van der Heijde 2006	etanercept vs. placebo	included
Inman 2008	golimumab vs. placebo	included
Barkham 2010	etanercept vs. placebo	included
Dougados 2011 SPINE	etanercept vs. placebo	included
Inman 2010	infliximab vs. placebo	excluded: low dose 3mg/kg (off label)
Huang 2013	adalimumab vs. placebo	included
Breban 2008	infliximab vs. infliximab on demand	excluded infliximab on demand
Li 2010	infliximab+MTX vs infliximab	excluded
Marzo-Ortega 2005	infliximab+MTX vs infliximab	excluded
Braun 2011	etanercept vs. sulfasalazine	excluded
Barkham 2009	infliximab vs. placebo	excluded: other target population HLAB27
Haibel 2008	infliximab vs. placebo	excluded: other target population (nr-axSpA)
Sieper 2010	adalimumab vs. placebo	excluded: other target population (nr-axSpA)
Navarro-Sarabia 2011	etanercept vs. placebo	excluded: high dose (off label)
Huang 2010/11/12	etanercept vs. placebo	excluded: 6 weeks
Cantini 2013	etanercept vs. placebo	excluded: long-term follow-up of patients in remission
Hu 2012	adalimumab vs. placebo	excluded: other end-point

5.3.1.2 Inclusion of studies from the period 1995-2005, based on McLeod 2007

Till November, 2005 nine studies identified by McLeod 2007[41] were screened for our enrolment criteria. The search strategy of Huang 2011[29] identified 9 randomized controlled trials on the use of anti TNF- antibodies in AS (see Table 2).

We excluded one study[10] as it examined the effect of etanercept at week 6. We have identifies in our search that the Wyeth study was published later as a paper by van der Heijde et al. in 2006, thus, we included this study as van der Heijde 2006 in the analysis.

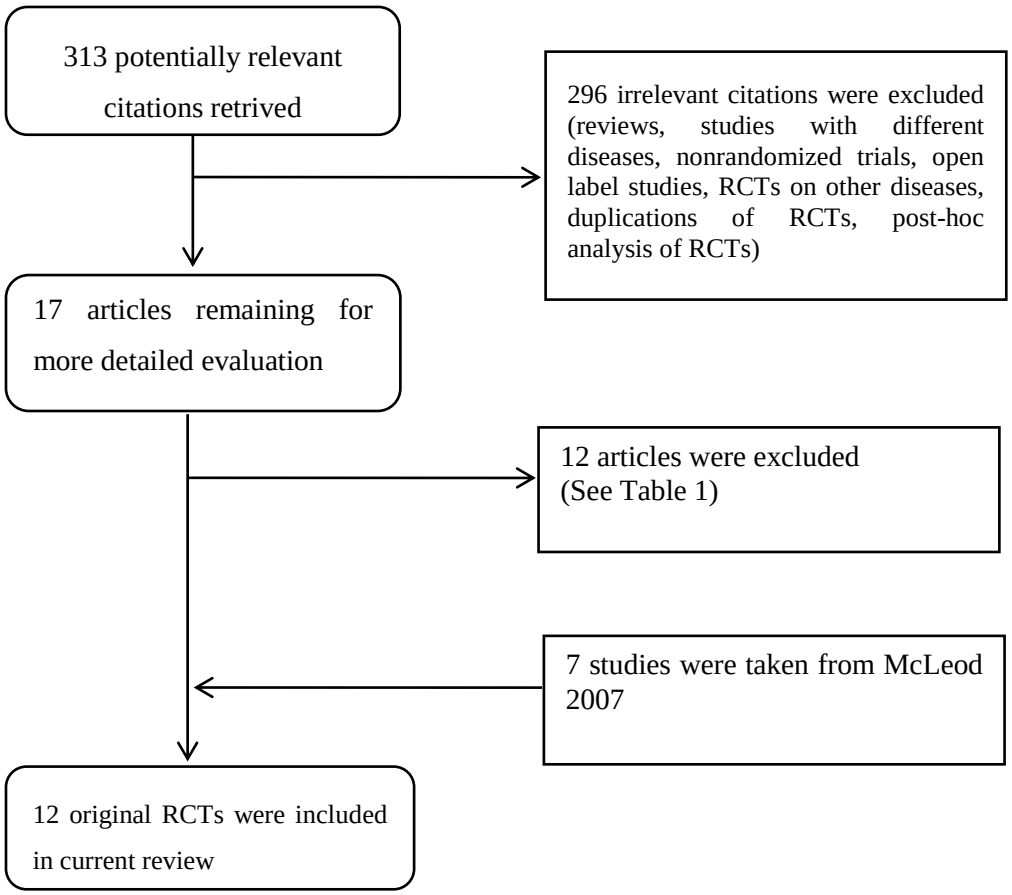
Out of the nine studies identified in McLeod 2007, we included two adalimumab studies[63 39], three etanercept studies[15, 17, 23], two infliximab studies[11, 61] in the meta-analysis.

Table 2 List of trials identified by McLeod 2007

References		Excl./Incl.
Braun 2002	infliximab vs. placebo	included
Gorman 2002	etanercept vs. placebo	included
Calin 2004	etanercept vs. placebo	included
Davis 2003	etanercept vs. placebo	included
Van der Heijde 2005 ASSERT	infliximab vs. placebo	included
Van der Heijde 2006 ATLAS	adalimumabvs. placebo	included
Maksymovich 2005 Canadian AS	adalimumab vs. placebo	included
Wyeth Study	etanercept 25mg vs. placebo	included as van der Heijde 2006

Altogether, we included 12 trials in our meta-analysis (see Figure 1).

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



5.3.2 Description of studies included in the meta-analysis

We included two infliximab studies[11, 61], three adalimumab studies[39 28, 63], six etanercept studies[4, 15, 17, 18, 23, 62] and one golimumab study[30] in the meta-analysis.

One infliximab study[61], one adalimumab study[63], one etanercept study[17] and one golimumab study[30] examined the effect of the therapy at week 24, while the rest examined the efficacy and safety of biological therapies during 12 weeks. However, most of the studies lasted 24 weeks reported endpoints also at week 12. In Heijde 2006 ATLAS and Inman 2008 patients could change to early escape in case the therapy was not efficient. The studies had different design, three studies examined monotherapy of biologics versus placebo[4, 15, 61], while the rest examined biologics in combination with conventional treatments.

In the following we shortly present the studies with infliximab included in the meta-analysis. The detailed descriptions of the studies included in the meta-analysis are presented in Appendix 8.5.

We also present the study design and results of infliximab studies not included in the meta-analysis.

5.3.2.1 Infliximab studies included in the meta-analysis

Two RCTs with infliximab[11, 61] encompassing at total of 348 patients were included in this review. The used comparator was the placebo in both RCTs. Primary endpoints were the BASDAI50 at week 12 and the ASAS20 response at week 24. The secondary endpoints were the following: ASAS40, ASAS partial remission, improvements in visual analogue score for spinal pain, BASFI, BASMI, SF36, the working group response criteria, concentration of C-reactive protein in serum, and erythrocyte sedimentation rate, disease activity, physical function, range-of-motion assessments, other musculoskeletal assessments, and quality of life.

5.3.2.1.1 Braun 2002[11]

Study characteristics: This trial was a multicentre, randomized, placebo controlled study, conducted in 11 centres in Germany. The analysis evaluated the effectiveness of infliximab, an antibody to tumour necrosis factor, in treatment of patients with active ankylosing spondylitis.

Treatment: Seventy patients were randomized to receive a blinded infusion of infliximab 5 mg/kg body weight or placebo at week 0, 2 and 6.

Patients' characteristics: Patients were excluded if they had active tuberculosis within the previous 3 years, specific changes in the radiograph of the chest at baseline, serious infections within the previous 2 months.

Endpoints: The primary endpoint was the improvement of disease activity by 50% between baseline and week 12, measured by BASDAI. The trial had some secondary endpoints: improvements in visual analogue score for spinal pain, BASFI, BASMI, SF-36, the working group response criteria, concentration of C-reactive protein in serum, and erythrocyte sedimentation rate.

Efficacy: Infliximab was effective in every criterion. Eighteen of 34 patients on infliximab had a regression of disease activity at week 12 of at least 50% compared with 3 of 35 on placebo. As a conclusion the authors stated that treatment with infliximab is effective in patients with active ankylosing spondylitis.

Safety: Three patients had to stop treatment because of adverse events.

5.3.2.1.2 Van der Heijde 2005 ASSERT[61]

Study characteristics: The Van der Heijde trial was a multicentre, randomized, double-blind, placebo-controlled study, conducted in 33 centres throughout the US, Canada, and Europe. The analysis evaluated the efficacy and safety of infliximab in patients with AS.

Treatment: In the study, 279 patients with ankylosing spondylitis were randomly assigned to receive infusions of placebo or 5 mg/kg infliximab at weeks 0, 2, 6, 12, and 18.

Patients' characteristics: Patients were excluded from the study if they had total ankylosis of the spine, any other inflammatory rheumatic disease, fibromyalgia, a serious infection within 2 months prior to randomization, tuberculosis or recent contact with a person with active

tuberculosis, infection within 6 months of screening. Previous treatment with anti-TNF therapy was prohibited.

Endpoints: The primary efficacy endpoint was the proportion of patients with a 20% improvement response according to the ASAS International Working Group criteria at week 24. Secondary end points included ASAS40 response, ASAS partial remission, disease activity, physical function, range-of-motion assessments, other musculoskeletal assessments, and quality of life.

Efficacy: Patients who received infliximab were more likely to have clinical response (61.2%) at week 24 than patients who received placebo (19.2%). Patients receiving infliximab also showed significant improvements in the BASDAI, BASFI, BASMI, chest expansion, and physical component summary score of the SF-36.

Safety: Adverse events in both treatment groups were mild or moderate. Adverse events were reported by 82.2% of patients receiving infliximab and by 72.0% of patients receiving placebo.

5.3.2.2 Infliximab studies not included in the meta-analysis

1) Infliximab on demand

Breban 2008[14]

Breban study was a randomized, controlled trial that assessed the efficacy of continuous treatment with infliximab with that of a treatment regimen adapted to symptom recurrence. Of 247 patients, 124 were assigned to receive infliximab every 6 weeks and 123 to receive on demand treatment. The primary end point was the proportion of patients who met the ASsessment in AS International Working Group criteria for 20% improvement at week 58. As a conclusion the authors stated that continuous treatment of AS with infliximab is more efficacious than on-demand treatment.

2) Infliximab+MTX

Li 2008[37]

Li trial was a randomized, controlled study. The study examined the short-term efficacy and safety of MTX in combination with infliximab compared with infliximab and placebo in the treatment of AS. Thirty-eight patients with active AS were randomized to receive MTX or

placebo for 22 weeks. The primary efficacy end-point was the percentage of ASAS20 responders after 30 weeks of treatment. Secondary end-points consisted of symptom improvement in individual ASAS domains and improvements in BASFI, BASDAI, CRP and Schober test at week 30, ASAS40 responders and lastly, the efficacy including partial remission of MTX at week 16. There were no significant differences between the two groups at any time points and the secondary outcome showed no significant differences between the two groups.

Marzo-Ortega 2005[40]

Marzo-Ortega trial was a single-centre, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of infliximab combined with methotrexate compared with methotrexate alone in the treatment of ankylosing spondylitis. Forty-two patients were randomized to receive five infusions of either 5 mg/kg infliximab or placebo over 30 weeks. The primary endpoint was improvement in disease activity as shown by the BASDAI at week 30. As a result, the authors stated that infliximab in combination with methotrexate was a safe and efficacious treatment, but the additionally received of methotrexate did not sustain response for 8 weeks.

3) Other study population

3A) Barkham 2008- HLA B27[3]

Barkham trial was conducted at the Leeds Teaching Hospitals Trust, Leeds, UK. This was a randomized, double-blind, placebo controlled study. The aim of the study was to assess the efficacy of infliximab in HLA–B27–positive patients with magnetic resonance imaging determined early sacroiliitis. Forty patients were randomised to receive infliximab 5 mg/kg or placebo at 0, 2, 6, and 12 weeks. The primary study end point was the change in the total MRI score from week 0 to week 16. Infliximab was an effective therapy for early sacroiliitis, providing a reduction in disease activity by week 16.

3B) SPA

Bosch 2002[60]

Bosch trial was a randomized, double-blind, placebo-controlled study that evaluated the efficacy profile of infliximab in short term treatment of patients with active spondylarthropathy (SpA). Forty patients with SpA were randomly assigned to receive an intravenous loading dose (weeks 0, 2, and 6) of 5 mg/kg infliximab or placebo. The primary end points of this study were the improvements in patient and physician global assessments of disease activity on a 100-mm visual analogue scale. Both primary end points improved significantly in the infliximab group, with no improvement in the placebo group.

5.3.3 Description of comparator studies

5.3.3.1 Adalimumab studies included in the meta-analysis

Three RCTs[28, 63, 39] with adalimumab encompassing at total of 741 patients were included in this review. The used comparator was the placebo in every RCT. The primary endpoint was the ASAS20 response at week 12. The secondary endpoints were the following: ASAS20 at week 24, SPARCC scores, ASAS40, ASAS5/6, high-sensitivity C-reactive protein (hs-CRP); percentage of patients achieving ASAS partial remission, BASDAI50, disease activity, pain and spinal mobility.

5.3.3.2 Etanercept studies included in the meta-analysis

The search yielded 6 RCTs[4, 15, 17, 18, 23, 62] with etanercept. Six RCTs with etanercept encompassing at total of 879 patients were included in this review. The used comparator was the placebo in every RCT. Primary endpoints were the ASAS20 at weeks 12 and 24, , BASDAI between randomisation and week 12, and in one study the change in AS-WIS[iii] at week 12[4]. The secondary endpoints were the ASAS5/6, ASAS partial remission, ASAS50 and

[iii] Ankylosing Spondylitis Work Instability Scale: a patient-derived outcome measure which allows stratification of the risk of job loss[4]

ASAS70, the physician's global assessment of disease activity, measures of spinal mobility, the C-reactive protein level, the BASDAI50, quality of life, functional ability BASFI, HAQ-DI, improvement in AS-DAS and AS-DAS status.

5.3.3.3 Golimumab study included in the meta-analysis

The search yielded one RCT[30] with golimumab. The RCT encompassing at total of 160 patients were included in this review. Placebo was used as comparator in the RCT. The primary endpoint was the ASAS20 criteria at week 14. The secondary endpoints were the ASAS 40% improvement (ASAS40), ASAS partial remission, and 20% improvement in 5 of 6 ASAS domains (ASAS5/6).

The number of trials in given comparisons might be different for each endpoint because of the distinct endpoint reporting across trials.

Table 3 Characteristics of included studies

Induction studies	N	Week	Treatment	Mean Age	Disease duration	HLA–B27 %	MONO/ Combined Therapy	Endpoints
Infliximab								
Braun 2002	69/70	12	infliximab 5mg/kg at week 0,2,6 n=34 2) placebo n=35	40.6 39.0	16.4 14.9	91 88	MONO	Primary: BASDAI50 at week 12 Secondary: improvements in visual analogue score for spinal pain, BASFI, BASMI, SF36, the working group response criteria, concentration of C-reactive protein in serum, and erythrocyte sedimentation rate
Van der Heijde 2005 ASSERT*	279	24	infliximab 5mg/kg kg at week 0,2,6,12,18 n=201 2) placebo n=78	40.0 41.0	7.7 13.2	86.5 88.5	MONO	Primary: number of ASAS20 responders at week 24 Secondary: ASAS40, ASAS partial remission, disease activity, physical function, range-of-motion assessments, other musculoskeletal assessments, and quality of life
Adalimumab								
Huang 2013	344	12	adalimumab 40mg eow n=229 2) placebo n=115	30.1 29.6	8.1 7.7	95.6 94.8	Combined	Primary: ASAS20 response criteria at week 12 Secondary: ASAS40, ASAS5/6, high-sensitivity C-reactive protein (hs-CRP), BASDAI50, disease activity, pain and spinal mobility
Van der Heijde 2006 ATLAS	315	12/24 rescuee	adalimumab 40mg eow n=208 2) placebo n=107	41.7 43.4	11.3 10.0	78.4 79.4	Combined	Primary: ASAS20 at week 12 Secondary: ASAS20 at week 24 and multiple measures of disease activity, spinal mobility, and function, as well as ASAS partial remission
Maksymovich 2005 (Lambert 2007)	82	12	adalimumab (40mg) n=38 2) placebo n=44	41.9 40.0	14.5 12.1	NR	Combined	Primary: ASAS20 response at week 12 Secondary: SPARCC scores
Etanercept								
Gorman 2002	40	12	etanercept 25mg twice weekly n=20 2) placebo n=20	38 39	15 12	95 90	Combined	Primary: ASAS20 at week 12 Secondary: the physician's global assessment of disease activity, measures of spinal mobility, the scores for enthesitis and peripheral-joint tenderness, the erythrocyte sedimentation rate, and the C-reactive protein level
Calin 2004	84	12	etanercept 25mg n=45 2) placebo n=39	45.3 40.7	15.0 9.7	NR	MONO	Primary: ASAS20 at week 12 Secondary: ASAS 50 and ASAS 70 responses and improved scores on individual components of ASAS, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), acute phase reactants, and spinal mobility tests

Davis 2003	277	24	etanercept 25mg twice weekly n=138 2) placebo n=139	42.1 41.9	10.1 10.5	84 84	Combined	Primary: ASAS20 at weeks 12 and 24 Secondary: achievement of the ASAS50 and ASAS70
van der Heijde 2006	356	12	etanercept 50 mg once weekly n=155 etanercept 25 mg twice weekly n=150 3) placebo n=51	41.5 39.8 40.1	9.0 10.0 8.5	NR	Combined	Primary: ASAS20 at week 12 Secondary: the proportion of responders based on ASAS 40 and ASAS 5/6 criteria at all time points, BASDAI, serum CRP
Barkham 2010	40	12	etanercept 25mg twice weekly n=20 2) placebo n=20	40.8 39.4	11 20	NR	MONO	Primary: change in AS-WIS at week 12 Secondary: assessments of disease activity (BASDAI), quality of life, functional ability (Bath Ankylosing Spondylitis Functional Index (BASFI), gait parameters using an electronic walkway and disability (Disability Index of Stanford Health Assessment Questionnaire (HAQ-DI)
Dougados 2011 SPINE	82	12	etanercept 50mg once weekly n=39 2) placebo n=43	46 48	19 23	79 86	Combined	Primary: BASDAI between randomisation and week 12 Secondary: ASAS20, ASAS40, ASAS5/6, ASAS partial remission, and improvement in BASDAI of at least 50% (BASDAI50), improvement in AS-DAS and AS-DAS status
Golimumab								
Inman 2008	356	14/24 rescue	golimumab 50mg every 4 weeks n=138 golimumab 100 mg every 4 weeks n=140 3) placebo n=78	38.0 38.0 41.0	11.0 9.5 16.0	81.8 84.3 84.6	Combined	Primary: ASAS20 criteria at week 14 Secondary: ASAS 40% improvement (ASAS40), ASAS partial remission, and 20% improvement in 5 of 6 ASAS domains (ASAS5/6)

*median, NR=not reported

Note: In some cases where the results were only presented as graphs, we read the results from the graphs (Braun 2002, Heijde 2006 ATLAS, Inman 2008).

5.3.4 Classical meta-analysis: efficacy and safety

5.3.4.1 Efficacy

In the meta-analysis we examine the efficacy of infliximab, adalimumab, etanercept and golimumab compared to placebo. We present the efficacy results at week 12 and at week 24 separately.

Efficacy results at week12

Two infliximab studies[11, 61], three adalimumab studies[39 28, 63], six etanercept studies[4, 15, 17, 18, 23, 62] and one golimumab study[30] reported efficacy results at week 12 on at least one of the efficacy endpoints examined in this study. No infliximab study has reported results on ASAS5/6 at week 12.

All the biological therapies examined in the study (infliximab, adalimumab, etanercept and golimumab) proved to be significantly superior to placebo treatment in terms of the efficacy end-points at week 12 (ASAS20, ASAS40, ASAS5/6, ASAS partial remission, BASDAI50% response). Results of the meta-analysis are presented in Table 4.

Table 4 Results of the direct comparison– efficacy at week 12

Treatment	Included studies	Included patients	RD (fixed effect)	RR (fixed effect)
ASAS 20 at week 12				
Infliximab vs. placebo	2	348	0.42 [0.32, 0.52]	2.92 [2.02, 4.21]
Adalimumab vs. placebo	3	741	0.35 [0.28, 0.42]	2.36 [1.90, 2.93]
Etanercept vs. placebo	5	839	0.34 [0.27, 0.41]	2.11 [1.75, 2.56]
Golimumab vs. placebo	1	216	0.38 [0.25, 0.50]	2.73 [1.75, 4.24]
ASAS 40 at week 12				
Infliximab vs. placebo	1	279	0.36 [0.26, 0.46]	3.80 [2.10, 6.90]
Adalimumab vs. placebo	2	659	0.31 [0.25, 0.37]	3.76 [2.56, 5.53]
Etanercept vs. placebo	3	478	0.28 [0.19, 0.38]	2.46 [1.63, 3.72]
Golimumab vs. placebo	1	216	0.30 [0.18, 0.41]	2.92 [1.68, 5.07]
ASAS 5/6 at week 12				
Infliximab vs. placebo	-	-	-	-
Adalimumab vs. placebo	2	659	0.40 [0.33, 0.46]	4.15 [2.90, 5.94]
Etanercept vs. placebo	2	438	0.35 [0.25, 0.45]	2.73 [1.77, 4.20]
Golimumab vs. placebo	1	216	0.42 [0.31, 0.52]	6.41 [2.92, 14.07]
ASAS Partial remission at week 12				
Infliximab vs. placebo	1	69	0.18 [0.03, 0.32]	7.21 [0.94, 55.50]
Adalimumab vs. placebo	2	659	0.18 [0.13, 0.22]	5.91 [2.92, 11.94]
Etanercept vs. placebo	2	438	0.18 [0.11, 0.25]	4.34 [1.74, 10.82]
Golimumab vs. placebo	1	216	0.18 [0.09, 0.27]	4.52 [1.66, 12.31]
BASDAI 50 at week 12				
Infliximab vs. placebo	1	69	0.44 [0.25, 0.64]	6.18 [2.00, 19.07]
Adalimumab vs. placebo	2	659	0.31 [0.25, 0.38]	2.93 [2.14, 4.02]
Etanercept vs. placebo	3	478	0.34 [0.24, 0.43]	2.80 [1.84, 4.27]
Golimumab vs. placebo	1	216	0.29 [0.17, 0.40]	2.87 [1.65, 5.00]

RR: In the case of values >1 the biological therapy is effective.
RD: In the case of positive values the biological therapy is effective.
Significant differences between treatments are indicated by bold letters.

Efficacy results at week 24

One infliximab study[61],one adalimumab study[63], one etanercept study[17] and one golimumab study[30] reported efficacy results at week 24 on at least one of the efficacy endpoints examined in this study. Davis 2003 did not report results on ASAS40 and ASAS 5/6 and BASDAI50% response efficacy endpoints.

The studies have different study-design. In Heijde 2006 ATLAS and Inman 2008 patients could change to early escape in case the therapy was not efficient. They reported results on the intention-to-treat population. Heijde 2005 ASSERT examined biologics in monotherapy, while the rest examined combined therapies.

According to the results of the meta-analysis, all the biological therapies achieved significantly better results at week 24 in treating AS, than placebo therapy. Results of the meta-analysis are presented in Table 5.

Table 5 Results of the direct comparison– efficacy at week 24

Treatment	Included studies	Included patients	RD (fixed effect)	RR (fixed effect)
ASAS 20 at week 24				
Infliximab vs. placebo	1	279	0.42 [0.31, 0.53]	3.18 [1.99, 5.08]
Adalimumab vs. placebo	1	315	0.32 [0.22, 0.42]	2.73 [1.80, 4.14]
Etanercept vs. placebo	1	277	0.34 [0.23, 0.45]	2.53 [1.80, 3.57]
Golimumab vs. placebo	1	216	0.33 [0.20, 0.45]	2.42 [1.57, 3.72]
ASAS 40 at week 24				
Infliximab vs. placebo	1	279	0.35 [0.25, 0.45]	4.01 [2.13, 7.55]
Adalimumab vs. placebo	1	315	0.34 [0.26, 0.42]	7.03 [3.17, 15.58]
Etanercept vs. placebo	-	-	-	-
Golimumab vs. placebo	1	216	0.28 [0.17, 0.40]	2.83 [1.62, 4.92]
ASAS 5/6 at week 24				
Infliximab vs. placebo	1	279	0.41 [0.31, 0.50]	6.27 [2.87, 13.71]
Adalimumab vs. placebo	1	315	0.33 [0.23, 0.42]	3.68 [2.16, 6.26]
Etanercept vs. placebo	-	-	-	-
Golimumab vs. placebo	1	216	0.28 [0.17, 0.39]	3.17 [1.71, 5.84]
ASAS Partial remission at week 24				
Infliximab vs. placebo	1	279	0.21 [0.15, 0.27]	17.46 [2.45, 124.51]
Adalimumab vs. placebo	1	315	0.17 [0.09, 0.24]	3.94 [1.74, 8.94]
Etanercept vs. placebo	1	277	0.12 [0.05, 0.19]	3.86 [1.62, 9.19]
Golimumab vs. placebo	1	216	0.21 [0.12, 0.30]	5.09 [1.88, 13.76]
BASDAI 50 at week 24				
Infliximab vs. placebo	1	279	0.40 [0.30, 0.50]	4.90 [2.51, 9.58]
Adalimumab vs. placebo	1	315	0.27 [0.18, 0.37]	2.83 [1.75, 4.57]
Etanercept vs. placebo	-	-	-	-
Golimumab vs. placebo	1	216	0.34 [0.22, 0.45]	3.39 [1.91, 6.03]

RR: In the case of values >1 the biological therapy is effective.
RD: In the case of positive values the biological therapy is effective.
Significant differences between treatments are indicated by bold letters.

5.3.4.2 Safety and tolerability

In the meta-analysis we examine the tolerability and safety of infliximab, adalimumab, etanercept and golimumab compared to placebo. In the safety analysis we did not distinguish the studies based on the duration (12 or 24 weeks). We used random effect models to calculate the confidence intervals as we found significant heterogeneity in most of the cases.

We have not found significant differences in safety and tolerability of biological treatments compared to placebo in terms of serious adverse events, adverse events leading to discontinuation of the therapy, infection, serious infection.

Nevertheless according to the results significantly more adverse events occur in adalimumab therapy groups compared to the placebo group. Injection-site reaction also significantly more frequently occurred with adalimumab and etanercept compared to placebo. The results are presents in Table 6.

Table 6 Results of the direct comparison– safety and tolerability

Treatment	Included studies	Included patients	RD (random effect)	RR (random effect)
Adverse events (AE)				
Infliximab vs. placebo	1	279	0.10 [-0.01, 0.22]	1.14 [0.98, 1.33]
Adalimumab vs. placebo	2	659	0.14 [0.07, 0.21]	1.32 [1.09, 1.61]
Etanercept vs. placebo	3	478	0.05 [-0.05, 0.15]	1.10 [0.93, 1.31]
Golimumab vs. placebo	1	216	0.08 [-0.03, 0.19]	1.11 [0.96, 1.28]
Serious AE				
Infliximab vs. placebo	1	279	0.01 [-0.04, 0.05]	1.30 [0.28, 6.12]
Adalimumab vs. placebo	2	659	-0.00 [-0.02, 0.01]	0.89 [0.26, 3.04]
Etanercept vs. placebo	4	483	0.01 [-0.02, 0.05]	1.56 [0.61, 3.94]
Golimumab vs. placebo	1	216	-0.03 [-0.09, 0.03]	0.56 [0.17, 1.87]
AEs leading to discontinuation of therapy				
Infliximab vs. placebo	2	348	0.03 [-0.08, 0.15]	1.57 [0.08, 30.88]
Adalimumab vs. placebo	2	659	0.01 [-0.00, 0.03]	1.73 [0.42, 7.16]
Etanercept vs. placebo	6	879	0.02 [-0.00, 0.05]	3.14 [0.60, 16.55]
Golimumab vs. placebo	1	216	0.02 [-0.02, 0.05]	2.23 [0.25, 19.62]
Infection				
Infliximab vs. placebo	1	279	0.07 [-0.06, 0.19]	1.18 [0.84, 1.66]
Adalimumab vs. placebo	2	459	0.05 [-0.05, 0.15]	1.34 [0.94, 1.90]
Etanercept vs. placebo	2	396	0.01 [-0.11, 0.13]	1.10 [0.74, 1.65]
Golimumab vs. placebo	1	216	0.10 [-0.04, 0.24]	1.28 [0.90, 1.80]
Serious infection				
Infliximab vs. placebo	1	279	0.01 [-0.01, 0.03]	1.87 [0.09, 38.55]
Adalimumab vs. placebo	2	459	-0.00 [-0.01, 0.01]	0.51 [0.05, 4.88]
Etanercept vs. placebo	-	-	-	-
Golimumab vs. placebo	1	216	-0.01 [-0.05, 0.02]	0.19 [0.01, 4.54]
Injection-site reaction				
Infliximab vs. placebo	1	279	0.02 [-0.06, 0.09]	1.17 [0.52, 2.62]
Adalimumab vs. placebo	1	315	0.07 [0.02, 0.12]	3.60 [1.10, 11.80]
Etanercept vs. placebo	5	839	0.14 [0.08, 0.20]	2.62 [1.77, 3.90]
Golimumab vs. placebo	1	216	0.06 [0.00, 0.12]	3.35 [0.77, 14.57]

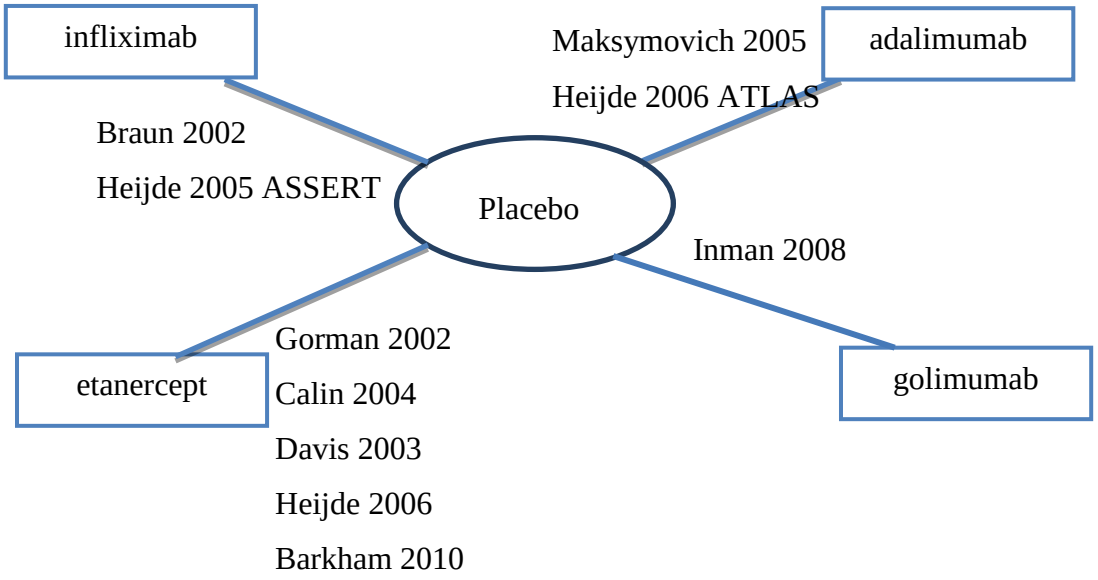
RR: In the case of values <1 the TNF therapy is safer.
RD: In the case of negative values the TNF therapy is safer.
Significant differences between treatments are indicated by bold letters.

Mixed treatment comparison: efficacy and safety

5.3.4.3 Treatment relations in the included studies

The same studies were included in the mixed treatment comparison as in the direct comparison (see Chapter 5.3.1.1 and Chapter 5.3.1.2). The relations between studies are presented in Figure 2.

Figure 2 Studies included in the mixed treatment comparison.



5.3.4.4 Results of the mixed treatment comparison

We have carried out indirect comparison of efficacy and safety of infliximab, adalimumab, etanercept and golimumab treatments.

The figures of this section present odds ratios between treatments A and B in the form treatmentA-treatmentB (Infliximab always considered as treatment A (the treatment on the first place) in the calculations). To read the figures:

- for ASAS20, ASAS40, ASAS5/6, ASAS partial remission, BASDAI50, if the point estimate is less 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 more 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.

5.3.4.5 Efficacy results at week 12

According to the results of the indirect comparison infliximab therapy was numerically superior to adalimumab, etanercept and golimumab therapies in terms of ASAS20, ASAS40 and BASDAI50 (OR<1), however the differences were not significant. Infliximab studies included in the analysis have not reported results for ASAS5/6 at week 12, thus infliximab is not included in the indirect comparison of ASAS5/6. In terms of partial remission infliximab showed similar results to other biologics.

No significant differences were found between other biologics either at week 12 in terms of ASAS20, ASAS40, ASAS5/6, ASAS partial remission, BASDAI50.

The results are presented in Figure 3, Figure 4, Figure 5, Figure 6, Figure 7.

Figure 3 Indirect comparisons, infliximab vs. biologics: Efficacy results – ASAS20 at week 12

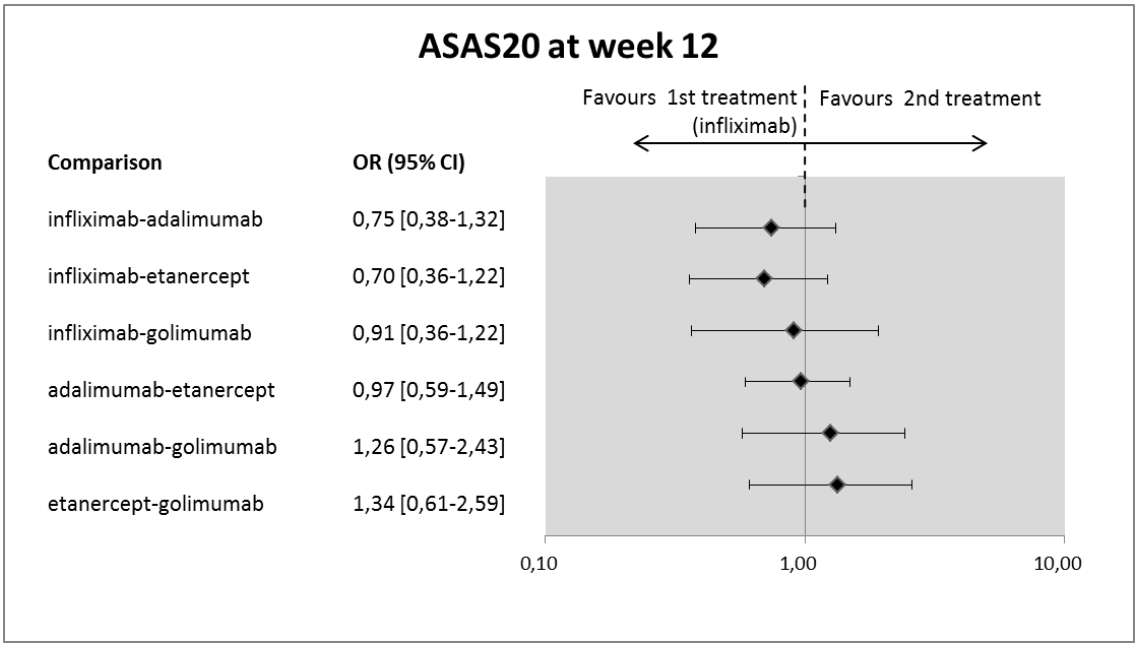


Figure 4 Indirect comparisons, infliximab vs. biologics: Efficacy results – ASAS40 at week 12

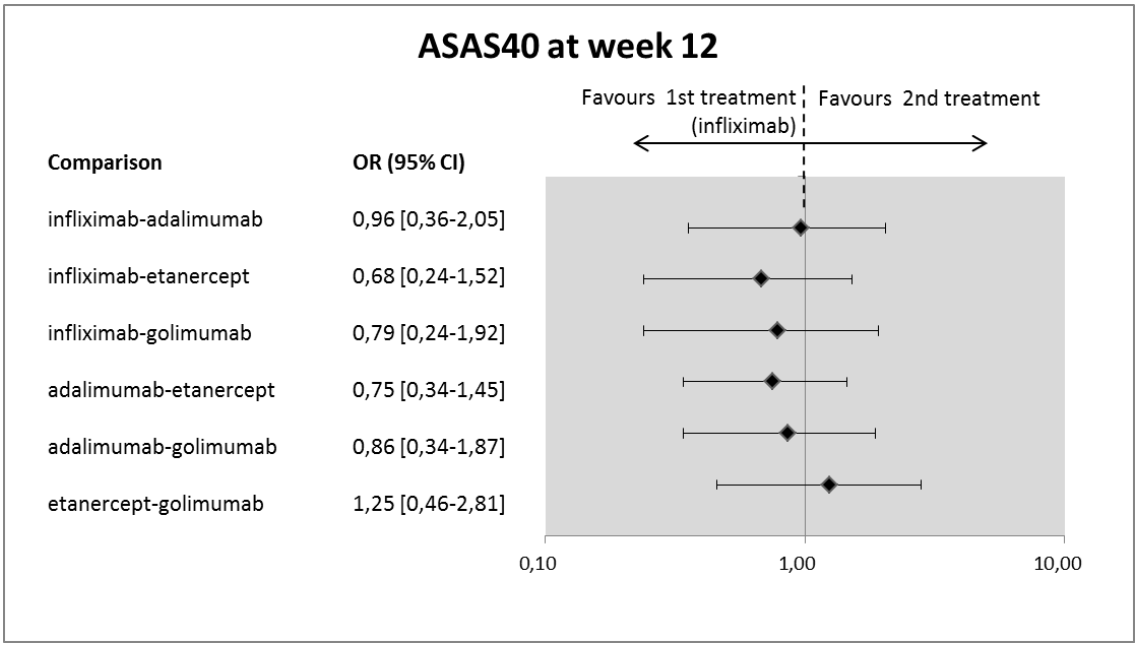


Figure 5 Indirect comparisons, infliximab vs. biologics: Efficacy results – ASAS5/6 at week 12

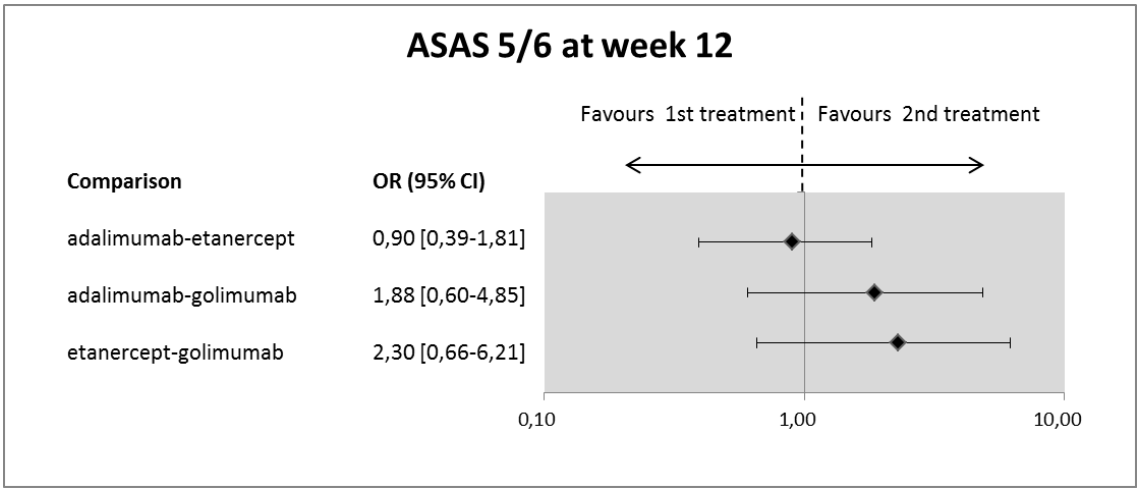


Figure 6 Indirect comparisons, infliximab vs. biologics: Efficacy results – ASAS partial response at week 12

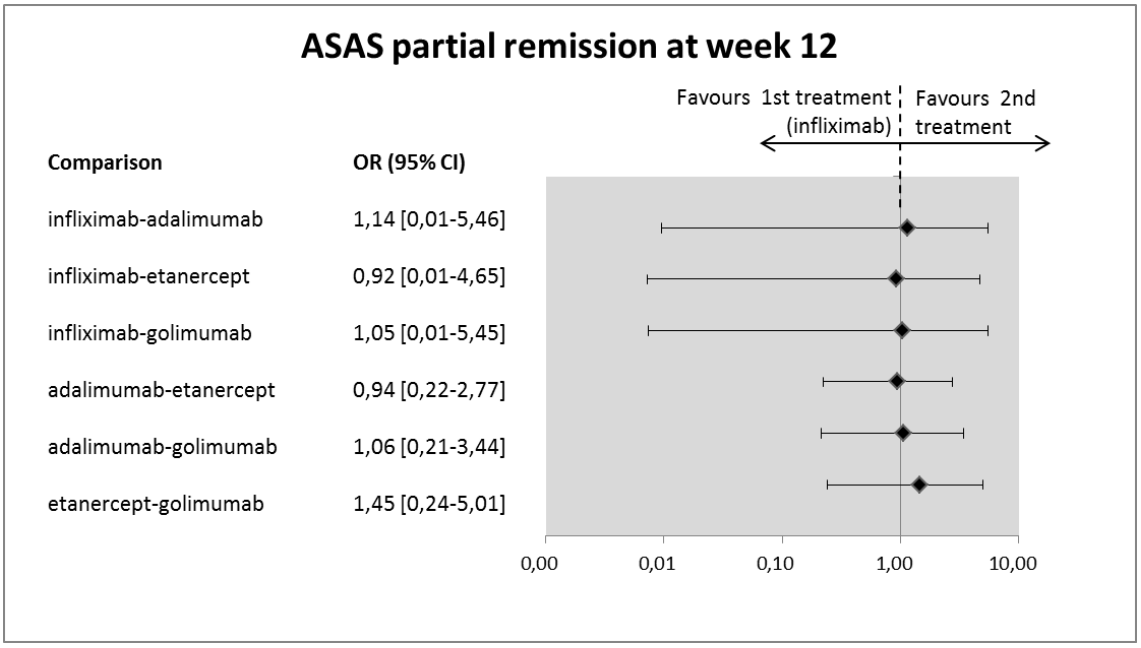


Figure 7 Indirect comparisons, infliximab vs. biologics: Efficacy results – BASDAI50 at week 12

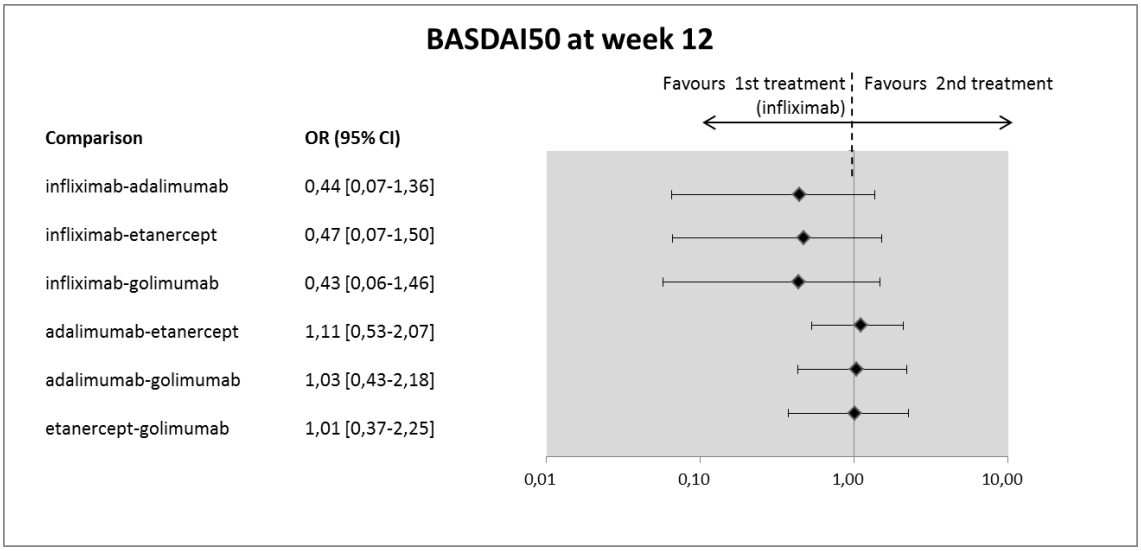
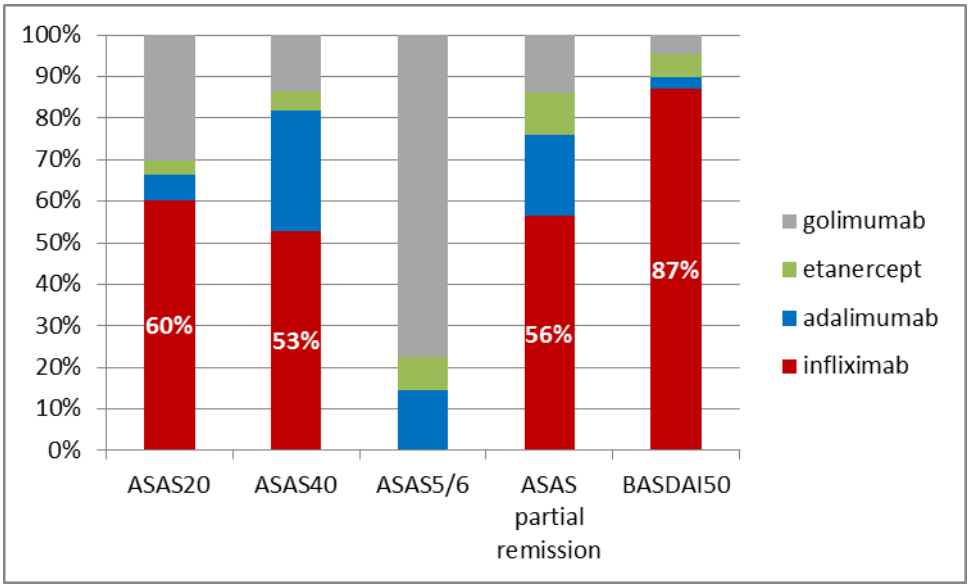


Figure 8 shows the probability of being the best treatment in terms of the five efficacy endpoints at week 12 for all the four biologics examined. Infliximab shows a 60% probability of being the best treatment of all in terms of ASAS20 improvement at week 12. Adalimumab, etanercept and golimumab show probabilities of 6%, 3% and 30%, respectively.

Figure 8 Indirect comparisons, infliximab vs. biologics: Probability of being the best treatment at week 12



Note: No infliximab studies reported results on ASAS5/6 endpoint.

5.3.4.6 Efficacy results at week 24

Infliximab therapy was numerically superior to adalimumab, etanercept and golimumab therapies in terms of all the efficacy endpoint at week 24 (except for ASAS40 compared to adalimumab), however the difference were not statistically significant. No significant differences were observed between other biologics either at week 24 in terms of ASAS20, ASAS40, ASAS5/6, ASAS partial remission, BASDAI50.

The results are presented in Figure 9, Figure 10, Figure 11, Figure 12, Figure 13.

Figure 9 Indirect comparisons, infliximab vs. biologics: Efficacy results – ASAS20 at week 24

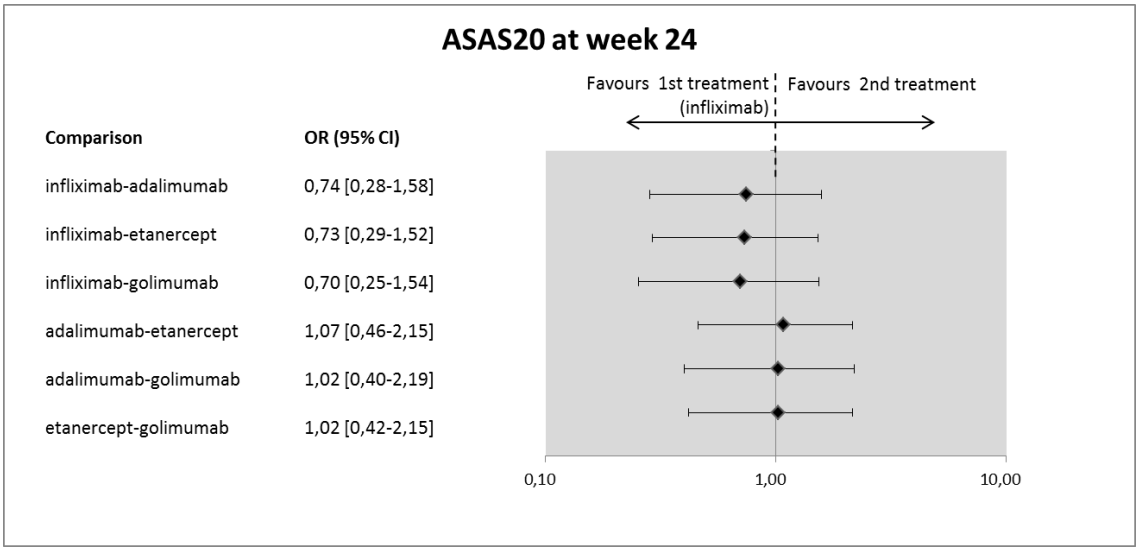


Figure 10 Indirect comparisons, infliximab vs. biologics: Efficacy results – ASAS40 at week 24

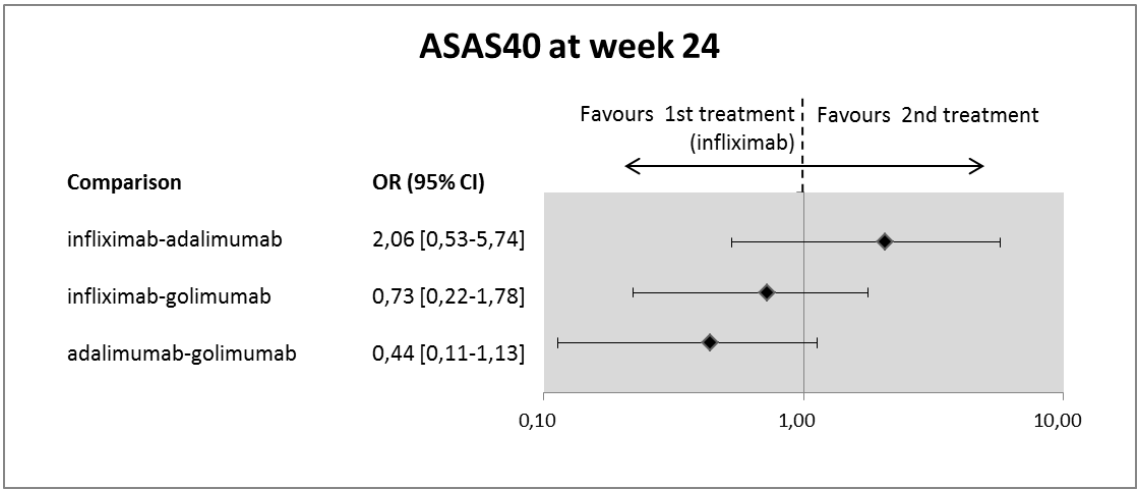


Figure 11 Indirect comparisons, infliximab vs. biologics: Efficacy results – ASAS5/6 at week 24

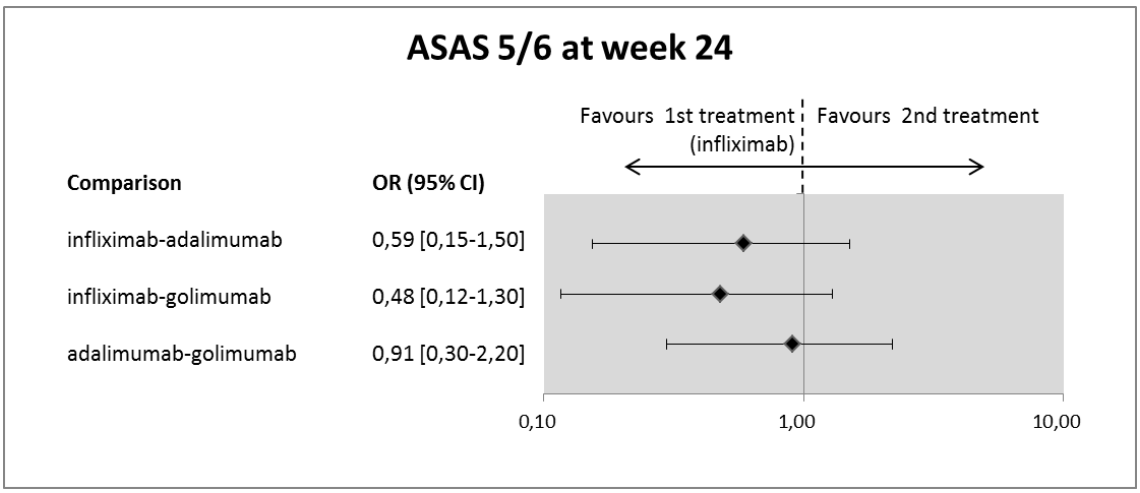


Figure 12 Indirect comparisons, infliximab vs. biologics: Efficacy results – ASAS partial response at week 24

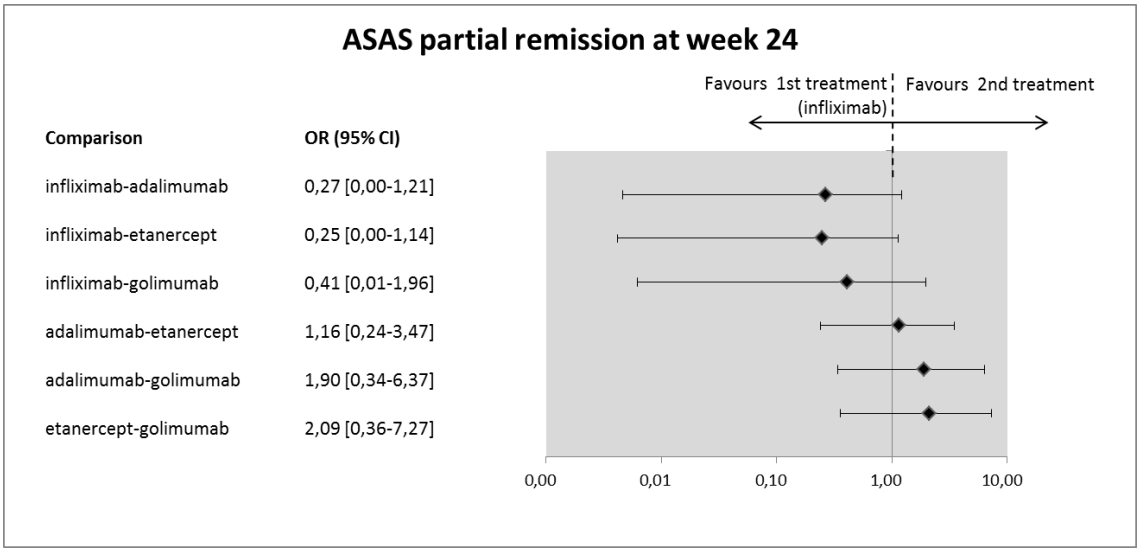


Figure 13 Indirect comparisons, infliximab vs. biologics: Efficacy results – BASDAI50 at week 24

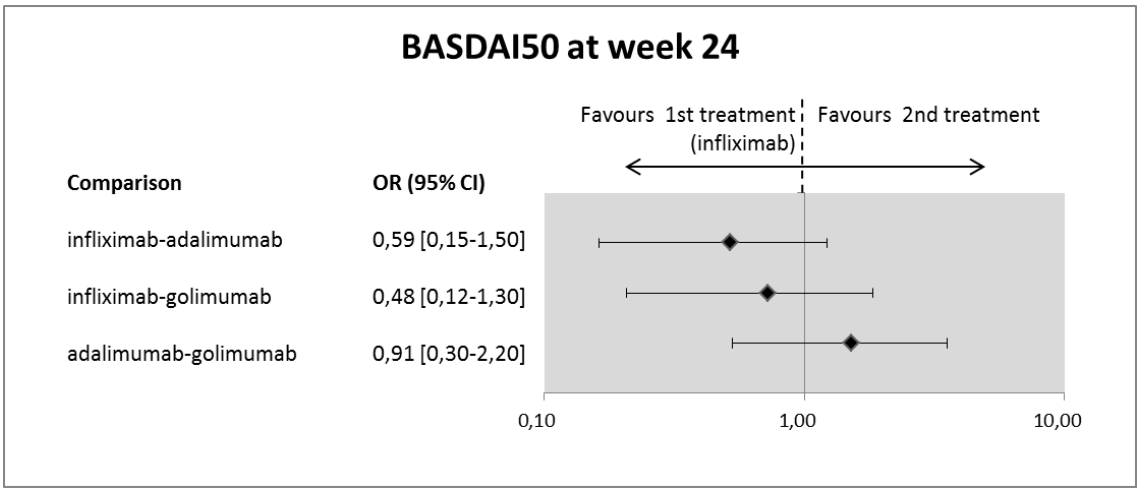
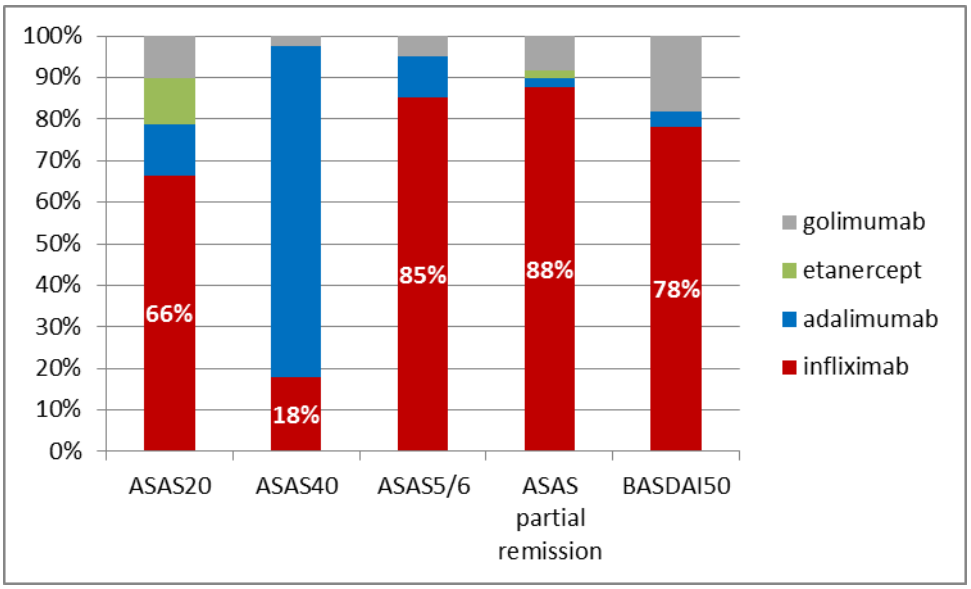


Figure 14 shows the probability of being the best treatment in terms of the five efficacy endpoints at week 24 for all the four biologics examined. Infliximab shows a 66% probability of being the best treatment of all in terms of ASAS20 improvement at week 12. Adalimumab, etanercept and golimumab show probabilities of 12%, 11% and 10%, respectively.

Figure 14 Indirect comparisons, infliximab vs. biologics: Probability of being the best treatment at week 24



Note: No infliximab studies reported results on ASAS5/6 endpoint.

5.3.4.7 Safety, tolerability

No significant differences were observed between infliximab and other biologics in terms of adverse events, serious adverse events, adverse events leading to the discontinuation of therapy, infection and injection site reactions (See Figure 15, Figure 16, Figure 17, Figure 18, Figure 19).

Figure 15 Indirect comparisons, infliximab vs. biologics: Safety results – Adverse events

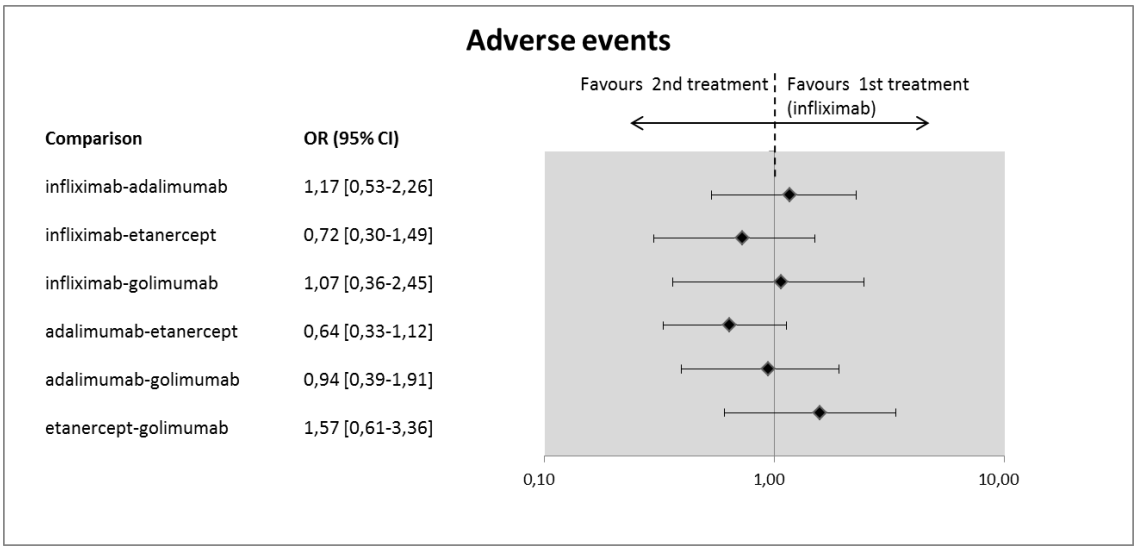


Figure 16 Indirect comparisons, infliximab vs. biologics: Safety results – Serious adverse events

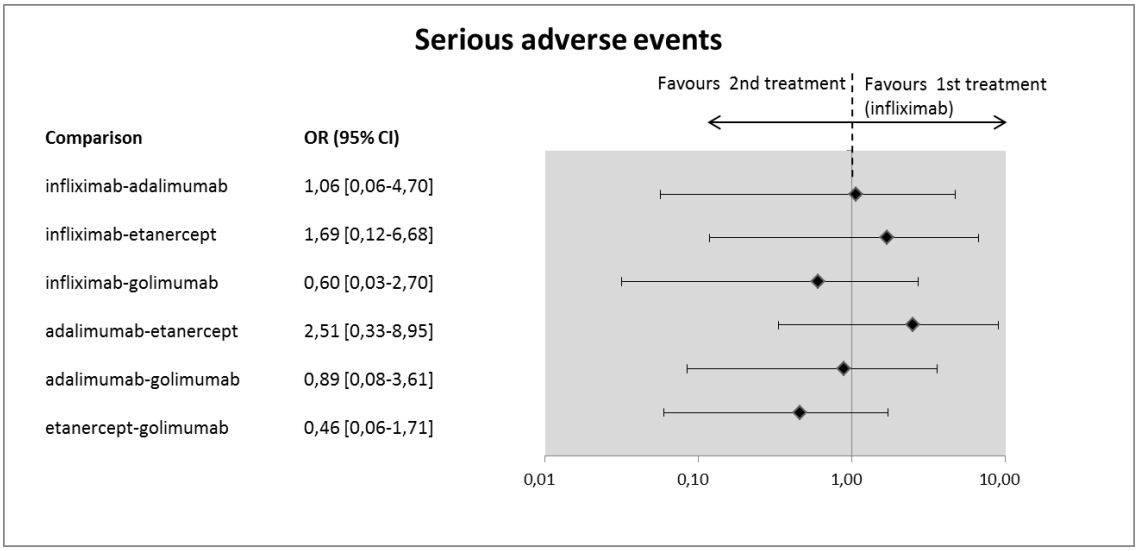


Figure 17 Indirect comparisons, infliximab vs. biologics: Safety results – Adverse events leading to discontinuation of therapy

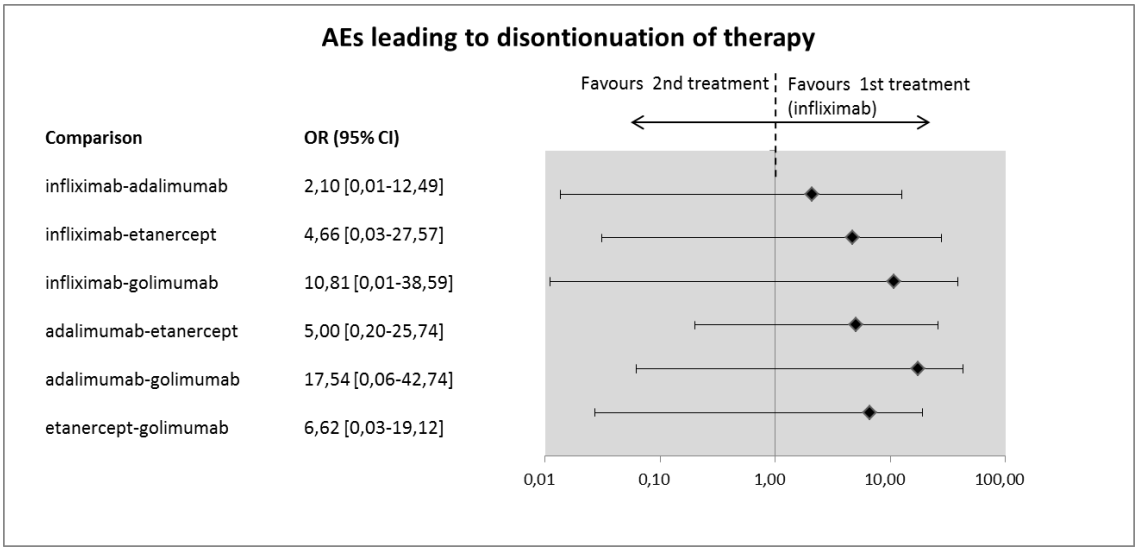


Figure 18 Indirect comparisons, infliximab vs. biologics: Safety results – Infections

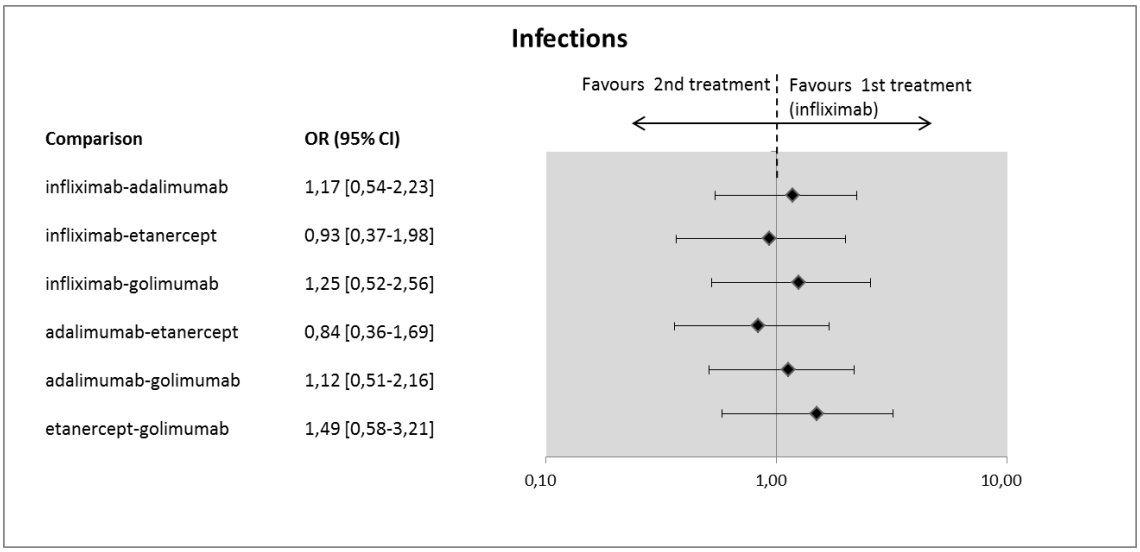
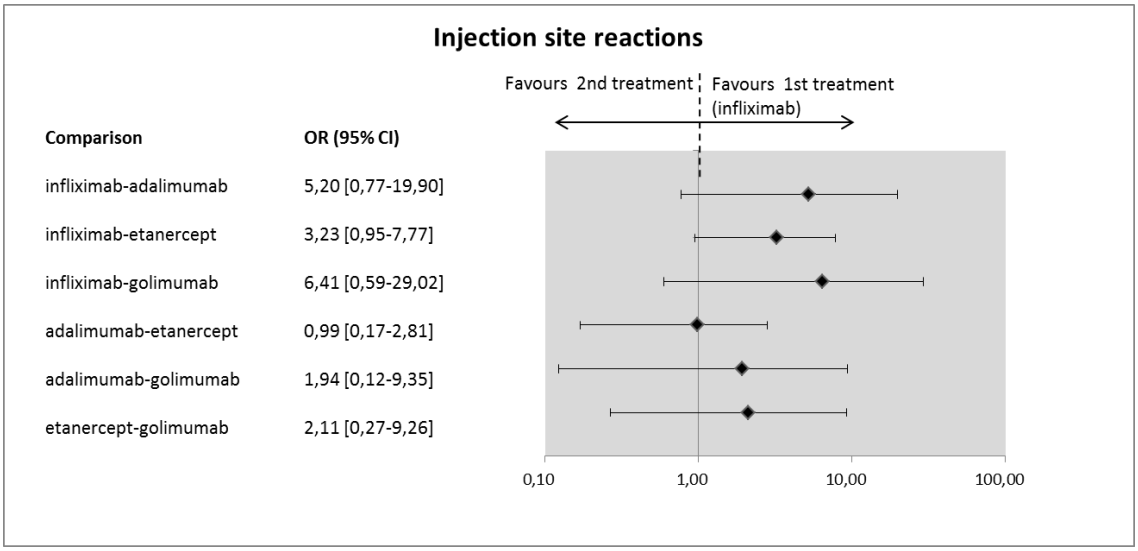


Figure 19 Indirect comparisons, infliximab vs. biologics: Safety results – Injection site reactions



5.4 *Review of previously published meta-analyses*

We conducted a simple MEDLINE search on meta-analysis with biologics in AS. In this chapter we shortly present the results of these meta-analyses.

McLeod 2007[41]- adalimumab, etanercept and infliximab

The objective of the study was to assess the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis (AS). The authors included nine placebo controlled RCTs in the meta-analysis (See Table 2). We used this study to identify RCTs, which meet our enrolment criteria, till November 2005. The end-points considered in the study ASAS 20, 50 and 70% improvement and mean change in BASDAI and BASFI at 12 weeks following initiation of anti-TNF-alpha therapy or placebo for all three drugs. Meta-analyses were also conducted at 24 weeks for etanercept and infliximab. According to the results of the meta-analysis "in the short term (12-24 weeks) the three treatments are clinically effective in relation to assessment of ASAS, BASDAI and BASFI over placebo/conventional treatment. Indirect comparisons of treatments were limited and did not show a significant difference in effectiveness between the three agents."

***Boyce 2010 - golimumab*[9]**

The goals of this article were to review the literature on the efficacy and safety of golimumab in RA, PsA and AS.

One clinical study was identified and used to evaluate the efficacy and tolerability of golimumab in patients with AS, where golimumab (subcutaneous) was more effective than placebo in terms of ASAS20 and ASAS40.

Regarding safety (considering all the three disease) "the incidence of any adverse effect appeared to be comparable in the GLM (61.2%-93.9%) and placebo groups (59.3%-85.3%), but withdrawals because of adverse effects were higher in the GLM groups (0%-12.1%) than in the placebo groups (0%-5.9%). The incidence of serious infections was comparable for GLM (0%-4.4%) and placebo (0.8%-3.5%). The most frequently reported adverse effects in the GLM groups were injection-site reactions (2.7%-37.1%), nausea (2.7%-22.9%), headache (3.8%-21.2%), nasopharyngitis (1.9%-15.0%), and upper respiratory tract infections (5.7%-13.8%)."

***Poddubnyy 2011 - adalimumab*[50]**

The objective of the study is to summarize the available data on short- and long-term efficacy and safety of adalimumab in the treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. The review included four adalimumab studies in AS (three of them were open-label studies). The authors find that "adalimumab is effective and reasonably safe in the short- and long-term treatment of patients with AS as well as patients with rheumatoid arthritis and psoriatic arthritis who do not respond to the standard therapy".

***Li 2012 – etanercept*[38]**

The objective of the study was to conduct meta-analysis to investigate the efficacy and safety of etanercept is AS and to compare the different responses between the Caucasian population and the Chinese population. The meta-analysis included fourteen randomized, double-blind, placebo-controlled clinical trials with 1,570 participants. The endpoints examined in the study were: ASAS20, ASAS40, ASAS5/6, and partial remission, BASFI, BASDI, BASMI, patient's global assessment, total back pain, nocturnal pain, chest expansion, morning stiffness, tender joint score, swollen join score, and occiput-to-wall as well as laboratory outcomes (CRP, ESR). According to the result "there was sufficient evidence to prove that etanercept has its advantages in both disease activity controlling and symptoms relieving, especially for axial joints compared with peripheric joints, without higher incidence of serious adverse events.

The preliminary analysis also provided that "the Caucasian population has better response to etanercept treatment, with more treatment-emergent adverse events."

***Migliore 2012 - adalimumab, etanercept and infliximab*[42]**

The objective of the study was to compare ASAS 20 response at 24 weeks between anti-TNF biological agents in patients with AS by means of a mixed treatment comparison of different randomized, controlled trials (RCTs) on the efficacy of biological therapies.

Altogether three RCTs were included in the mixed treatment analysis. According to the results, anti-TNF agents demonstrated to be more efficacious in inducing an ASAS20 response than placebo. "Infliximab shows a 72% probability of being the best treatment of all. Adalimumab and etanercept show probabilities of 13% and 15%, respectively. No differences were observed when comparing directly an anti-TNF-α agent against another. When compared with placebo, Infliximab increases the probability of response by ~7-times (OR = 6.8), Adalimumab by ~4-times (OR = 4.4), and Etanercept by 5-times (OR = 4.9)."

***Thaler 2012 - Drug Class Review: Targeted Immune Modulators*[57]**

Thaler 2012 systematically compared the efficacy, effectiveness, and safety (adverse events) of abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, and ustekinumab in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis based on literature published between 2009 (January) to 2011 (October).

According to the authors the "targeted immune modulators are highly effective medications for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis that substantially improve the burden of disease and are generally safe for short-term treatment".

***Baraliakos 2012*[2]**

Baraliakos et al. performed a literature review as basis for the update of the Assessment in SpondyloArthritis international Society/European League Against Rheumatism (ASAS/EULAR) treatment recommendations with biologics in AS.

According to their results 98 papers contained efficacy data and 25 had complete data for analysis. "The treatment effect sizes (95% CI) for anti-TNF vs placebo varied between 0.34

(0.08, 0.6) and 1.5 (0.45, 2.5) for BASDAI and 0.33 (0.07, 0.59) and 2.5 (1.3, 3.7) for BASFI. The calculation of the numbers needed to treat all the different outcomes varied between 2.3 and 3.0 patients for all ASAS outcomes and between 2.7 and 6.5 patients for ASAS partial remission. Data on biologics other than anti-TNF and for TNF blockers on juvenile SpA were limited. The incidence rates of uveitis during anti-TNF treatment varied between 4.4/100 patient-years (pys) and 15.6/100 pys during placebo ($P < 0.05$). The incidence rates of IBD flares were significantly less during infliximab treatment (0.2/100 pys). The rate of infections was higher in patients treated with anti-TNF as compared with placebo, but there was no difference in the incidence of serious infections for treatment with anti-TNF vs placebo".

5.5 Conclusions

5.5.1 Efficacy and safety

Our review delivers both direct and indirect comparisons of the efficacy and safety of four biologics for ankylosing spondylitis from double-blind, placebo-controlled trials. Firstly, a classical direct meta-analysis was undertaken to obtain summary estimates of clinical effectiveness and safety. Following recent NICE guidelines, a mixed treatment comparison was undertaken allowing for indirect comparisons in the absence of head-to-head trials.

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

Generally, biologics showed similar efficacy and safety profile. The meta-analysis showed that all biologics demonstrated statistically significant improvements compared to placebo with respect to ASAS20, ASAS40, ASAS5/6, ASAS partial remission, BASDAI50 improvements both at week 12 and 24. Regarding safety, we have not found significant differences between biologics and placebo treatments either in terms of adverse event, serious adverse events, adverse events leading to the discontinuation of the therapy, infection, and serious infection. According the results of the mixed treatment comparison no significant differences were observed between the different types of biologic treatments in terms of the efficacy and safety endpoints examined in the study.

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 (e.g. in the analysis we did not distinguish between mono and combined therapies).

6 Biological therapies for the treatment of AS – systematic review of the health economic literature

Summary

The cost-utility of infliximab, etanercept, adalimumab and golimumab was analysed in the UK, The Netherlands, Spain, France, Germany and Canada. Among the biologicals, infliximab was the most frequently studied. Depending on model assumptions the incremental cost-effectiveness ratio (ICER) varied broadly. Available cost-utility analyses suggest that anti-TNF therapies are cost-effective treatments in AS in these European countries. Nevertheless, most of the studies included only one biological drug which was compared to conventional treatment, thus we cannot draw conclusion regarding the comparative cost-effectiveness of different biologicals and the optimal anti-TNF treatment sequence.

For countries from Central and Eastern Europe, cost-utility data are lacking regarding biological treatment of AS. Transferability of cost-effectiveness findings from one country to another is limited, thus country-specific evaluations are required to take into account country-specific features.

6.1 Literature search

Our aim was to systematically review the literature for health economic evaluations of adalimumab, etanercept, golimumab and infliximab for the treatment of AS.

Gaujoux-Viala et al. performed a systematic literature review for articles published up to November 2010, we rely on findings of this extensive report.[22]

We have performed a complementary search for the time period between November 2010 and March 2013 which 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. The search strategies applied are presented in Appendix 8.7. Additionally, the

websites of the National Institute for Health and Care Excellence (NICE) and Canadian Agency for Drugs and Technologies in Health (CADTH) were search for relevant reports.

Original articles of full economic evaluations presenting cost-utility data (cost/QALY) of biological therapies (adalimumab, etanercept, golimumab, infliximab) for AS were retrieved by two independent reviewers. Articles with full text in English were analysed and a short descriptive summary of each is provided.

6.2 Results

The review by Gaujoux-Viala et al. discussed ten articles analysing the health economics of adalimumab, etanercept, infliximab. One article was excluded from our report as that was not a cost-utility analysis.[5] Altogether nine articles were considered from this review for the current HTA report.[1, 7, 8, 20, 33-36, 44]

The number of hits of the complementary literature search 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 – 7 hits / 0 articles included
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations – 3 hits / 0 articles included
- Web of Knowledge – 39 hits / 1 article included
- National Institute for Health and Care Excellence (NICE) - 1 report included
- Canadian Agency for Drugs and Technologies in Health (CADTH) - 0 report included

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

In the next sections we present the nine cost-utility studies (up to November 2010) discussed by Gaujoux-Viala et al.[22] and introduce the two publications from our additional search (2010-2013).

6.2.1 Systematic review by Gaujoux-Viala et al. (2012)

Nine articles reporting the cost-utility of TNF inhibitors in AS patients have been published: five for infliximab[20, 33-36], one infliximab or etanercept against conventional treatment[7], two for etanercept[1, 44], and one for adalimumab[8].

Kobelt et al, UK (2004)[33]

Kobelt et al examined the use of infliximab in the UK with a 2-year time horizon in the base case analysis and a 30-year time horizon in sensitivity analyses from a societal perspective. Treatment increased the number of QALYs by 0.175, leading to a cost per QALY gained of £35 400 for the first year of treatment. When treatment was assumed to continue for the full 2 years the cost per QALY was £32,800. When infliximab infusions were given every 8 weeks instead of every 6 weeks, the cost per QALY was reduced to £17,300. In the long-term model, the cost per QALY was estimated at £9,600.

Kobelt et al, Canada (2005)[34]

The UK model (Kobelt 2004) was adapted to examine the use of infliximab in Canada. Over a 30-year time frame the cost per QALY gained in the societal perspective was $Can37,491. Assuming that disease in patients on treatment progresses at half the rate of that of untreated patients, the cost-effectiveness ratio was $Can45,121, and with the most conservative assumption that disease progression is the same in both arms, the ratio was $Can54,137. The results were sensitive to the dosing regimen adopted, the discontinuation rate and the assumptions concerning disease progression while on treatment.

Boonen et al, The Netherlands (2006)[7]

This analysis examined the use of infliximab or etanercept in the Netherlands from a societal perspective. Markov model over five years with cycle times of three months was computed. Utilities and costs assigned to the BASDAI disease states were derived from a two year observational Dutch cohort. The incremental cost-utility ratios (ICURs) varied from €67,207 to €237,010 for infliximab as compared with usual care. The ICUR for etanercept was

between €42,914 and €123,761 per QALY for etanercept compared with usual care. The model was sensitive to drug prices.

Kobelt et al, UK (2007)[35]

Kobelt et al. compared the cost effectiveness of treating AS with infliximab in the UK over a lifetime using a Markov model, with data estimated from two different clinical trials and adjusted for clinical practice guidelines. From the societal perspective and under the assumption that disease activity would be controlled and functional capacity would remain stable while on the drug, treatment with infliximab dominated standard treatment. From the UK National Health Service perspective, the cost per QALY gained over a lifetime was £28,300 and £26,800 for the two trials. If functional capacity were to deteriorate at half the rate of that for untreated patients the cost per QALY gained would be £35,300 and £34,100, respectively. Results were sensitive to the dosing regimen adopted, the discontinuation rate and the assumptions concerning disease progression while on treatment.

Ara et al, UK (2007)[1]

A mathematical model based on BASDAI and BASFI was constructed to estimate the costs and benefits associated with etanercept plus NSAIDs as compared with NSAIDs alone in the UK. Individual patient data from phase III RCTs trials were used to inform the proportion and magnitude of initial response to treatment and changes in health related quality of life. Over a 25-year time horizon, etanercept plus NSAIDs gave 1.58 more QALYs at an additional cost of £35,978 as compared with NSAIDs alone. This finding equates to an estimate of £22,700 per QALY. The ICER (cost per QALY) with shorter time periods was £27,600, £23,600 and £22,600 at 2, 5 and 15 years, respectively. With a 25-year time horizon, 93% of results from the probabilistic analyses fell below a threshold of £25,000 per QALY.

Kobelt et al, Spain (2008)[36]

The Kobelt model (2007, UK) was adapted to examine the use of infliximab in Spain. Cost-effectiveness estimates were based on a placebo-controlled clinical trial and an open clinical study in Spain. From the societal perspective, infliximab treatment dominated standard treatment in both analyses. From the perspective of the healthcare system, with the

assumption that over the long term the functional ability of patients on treatment would decline at half the natural rate, the cost per QALY gained was estimated at €22,519 (double-blind trial) and €8866 (open study). Assuming that patients' function on treatment remains stable, the cost-effectiveness ratios were €15,157 and €5,307, respectively. Under the most conservative assumption (no effect of treatment on progression), the ratios were €31,721 and €13,659, respectively. In addition, the results were sensitive to the time horizon and discontinuation rates.

Fautrel et al, France (2010)[20]

A recent study in France compared two therapeutic regimens: infliximab every 6 weeks and on demand, for AS. Data were collected by phone every 3 months for 1 year, direct and indirect costs were calculated from a payer perspective. Health-related quality of life was assessed by a general health rating scale. The ICERs for every 6 weeks in comparison to the on-demand regimen was €50,760 for one QALY gained.

Neilson et al, Germany (2010)[44]

The model by Ara et al (2007) was adapted to examine the use of etanercept in Germany. In the base case, etanercept plus usual care yielded 1,475 more QALYs at an additional cost of €80 827,668 (social health insurance perspective) or €32 657,590 (societal perspective), for an ICER of €54,815 per QALY and €22,147 per QALY, respectively. Over a shorter time horizon of 10 years, the ICERs were €59,006 and €29,815 for social health insurance and societal viewpoints, respectively. Assumptions having the largest impact on results included withdrawal rates from etanercept, quality of life, disease costs and initial response.

Botteman et al, UK (2007)[8]

This study evaluated the cost-effectiveness of adalimumab versus conventional therapy in patients with AS and used pooled data from two phase III studies of adalimumab in active AS. The central estimate was that, over 30 years, adalimumab therapy yielded 1.03 more QALYs per patient. Some AS treatment-related costs were estimated to be offset by adalimumab (at £10,750/patient), for a total incremental cost (adalimumab vs conventional therapy) of

£23,857 per patient. The 30-year ICER of adalimumab versus conventional therapy was estimated at £23,097 per QALY. When applying societal perspective (indirect costs were included), the ICER improved to £5,093 per QALY.

6.2.2 Articles revealed by the additional search

Riemsma et al, UK (2011)[51]

In this report the manufacturer analysis the cost-utility of golimumab in AS using a de novo economic model were published. The model compares:

- golimumab 50 mg given once a month, on the same date each month against three different treatments:

- adalimumab (40 mg adalimumab administered every other week as a single dose),

- etanercept (25 mg administered twice weekly, or 50 mg administered once weekly),

- conventional therapy (non-biologic DMARDs, NSAIDs, Cox-2 inhibitors, and physiotherapy).

In the base-case model, a decision is made to continue or withdraw from TNF-α inhibitors according to probability of response defined as 50% improvement in BASDAI at 12 weeks. After the initial decision tree, patients enter a Markov model with a cycle length of 12 weeks and a time horizon in the base case of 20 years (maximum 60.1 years (up to age 100)). If patients are on TNF-α inhibitors, they either stay on therapy („On treatment"), or discontinue due to lack of efficacy or adverse events („Not on TNF-α"). To model the lower disease activity just after discontinuation of TNF-α inhibitor therapy two 12-week tunnel states („Just discontinued" and „Discontinued") were incorporated in the model. Patients in the conventional treatment arm enter the Markov model in the „Not on TNF-α" state. Patients can die at any point in the model. SAEs and injection site reactions of TNF-α inhibitors treatments are included in the model. In the base case analysis the costs and QALYs of golimumab were comparable to those of the other TNF-α inhibitors. The ICER of golimumab versus

conventional care is £26,597. Adalimumab and etanercept are extended dominated by golimumab. The evidence review group highlights that based on rates for discontinuation and adverse events from the mixed treatment comparison and with model corrections made, golimumab is less effective than the other two TNF-α inhibitor treatments and would not be cost effective at any willingness to pay threshold. This does not preclude there being value in the use of golimumab as second-line therapy. The current model structure does however not allow the evaluation of sequential use of golimumab.

Tran-Duy et al., The Netherlands (2011)[58]

Long-term quality of life, societal costs and cost- effectiveness as affected by sequential drug treatment strategies for AS was modelled in The Netherlands. Discrete event simulation paradigm was selected for model development and societal perspective was used for the analysis. Drug efficacy was modelled as changes in BASDAI and BASFI which were linked to costs and health utility using statistical models fitted based on an observational AS cohort. Clinical efficacy was based on clinical data. Two strategies were compared: (1) five available non-steroidal anti-inflammatory drugs (strategy 1) and (2) same as strategy 1 plus two tumour necrosis factor α inhibitors in a random order for each patient (strategy 2). The time horizon was 70 years with intervals of 1–3 months. Incremental cost per QALY gained in strategy 2 compared with strategy 1 was €35,186. At a willingness-to-pay threshold of €80,000, it was 99.9% certain that strategy 2 was cost-effective.

6.3 Discussion, conclusions

The cost-utility of infliximab, etanercept, adalimumab and golimumab was analysed in various studies from the UK, The Netherlands, Spain, France, Germany and Canada. Most of the studies compared anti-TNF treatment with conventional therapy. Among the biologicals, infliximab was the most frequently studied: UK 2, The Netherlands 1, Spain 1, France 1, Canada 1 study.

Depending on model assumptions (time horizon, drug price, dosing regimens, discontinuation rate, assumptions concerning disease progression while on treatment, perspective of the analysis) the incremental cost-effectiveness ratio (ICER) varied broadly.

In the UK, taking societal perspective, the ICER of infliximab compared to conventional treatment was £35,400 per QALY for the first year of treatment, but when treatment was assumed to continue for 2 years, the cost per QALY was £32,800. When infliximab infusions were given every 8 weeks instead of every 6 weeks, the cost per QALY was reduced to £19,400. The ICER was £9,600/QALY on the 30-years horizon.[33] In another analysis from the UK, infliximab dominated standard treatment on the life-time horizon from the societal perspective, and ICER was £28,300 and £26,800 from the NHS perspective. The ICER of etanercept vs. conventional treatment in the UK from the NHS perspective was £27,600, £23,600 and £22,600 per QALY at 2, 5 and 15 years, respectively.[1] The 30-year ICER of adalimumab vs. conventional therapy in the UK from the NHS perspective was estimated at £23,097 per QALY, and £5,093 per QALY from the societal perspective.[8]

In The Netherlands, taking societal perspective the ICER varied from €67,207 to €237,010 for infliximab as compared with usual care, and the ICER was between €42,914 and €123,761 per QALY for etanercept compared also with usual care.[7]

In France, two treatment strategies of infliximab were compared: every 6 weeks vs. on demand, the ICER of the every 6 weeks strategy was €51,000 per QALY.[20]

In Germany, ICER of etanercept vs. usual care on a 25-year horizon was €54,815 per QALY (social health insurance perspective) and €22,147 per QALY (societal perspective), respectively.[44]

In Spain, taking the societal perspective infliximab treatment dominated standard treatment and from the perspective of the healthcare system, the cost per QALY gained was estimated at €8,866 - €22,519 on a 40-year horizon.[36]

Two studies considered more than one biological drug. In the UK, cost-utility of golimumab was analysed against two other anti-TNF treatment strategies (adalimumab and etanercept) and conventional treatment, however infliximab was not considered as a comparator. In this analysis the ICER of golimumab versus conventional care was £26,597 and adalimumab and etanercept were extended dominated by golimumab.[51] In The Netherlands a treatment including five available NSAIDs was compared to a treatment with two TNF-alfa inhibitors (one subcutaneously and one intravenously administered drug randomly chosen from two possible drugs) in a random order for each patient on a 70-years horizon, and the ICER of the latter was €35,186.[58]

To sum up, available cost-utility analyses suggest that anti-TNF therapies are cost-effective treatments in AS in the UK, Germany, Spain, Germany and The Netherlands. We find important to highlight two aspects. Not all biological were studied in all the five countries. Furthermore, most of the studies included only one biological drug which was compared to conventional treatment. The only analysis which compared different biological treatment arms did not cover the whole available spectrum of anti-TNF therapies.[51] Therefore, we cannot draw conclusion regarding the comparative cost-effectiveness of different biologicals and the optimal anti-TNF treatment sequence.

For countries from Central and Eastern Europe, health economics data are lacking regarding biological treatment of AS. Transferability of cost-effectiveness findings from one country to another is limited, thus country-specific evaluations are required to take into account country-specific features such as treatment policies, epidemiology of AS, service patterns and unit costs.

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8 Appendices

8.1 Search terms for RCTs and meta-analyses

((("spondylitis, ankylosing"[MeSH Terms] OR ("spondylitis"[All Fields] AND "ankylosing"[All Fields]) OR "ankylosing spondylitis"[All Fields] OR ("ankylosing"[All Fields] AND "spondylitis"[All Fields])) OR ("spondylitis, ankylosing"[MeSH Terms] OR ("spondylitis"[All Fields] AND "ankylosing"[All Fields]) OR "ankylosing spondylitis"[All Fields] OR ("ankylosing"[All Fields] AND "spondyloarthritis"[All Fields]) OR "ankylosing spondyloarthritis"[All Fields]) OR ("spondylitis, ankylosing"[MeSH Terms] OR ("spondylitis"[All Fields] AND "ankylosing"[All Fields]) OR "ankylosing spondylitis"[All Fields] OR ("ankylosing"[All Fields] AND "spondyloarthritides"[All Fields])) OR ("spondylarthritis"[MeSH Terms] OR "spondylarthritis"[All Fields] OR "spondylarthritides"[All Fields])) AND (("adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields]) OR ("infliximab"[Supplementary Concept] OR "infliximab"[All Fields]) OR ("golimumab"[Supplementary Concept] OR "golimumab"[All Fields]) OR ("TNFR-Fc fusion protein"[Supplementary Concept] OR "TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields])) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[MeSH Terms] OR randomly[tiab] OR trial[ti]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))

8.2 Search results and study selection

Table 7 Search results and study selection (01.07.2007-20.04.2012)

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References	Excl./Incl.
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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.[32]. 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 program code

```
# Binomial likelihood, logit link
# Fixed effects model
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
    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
# model for linear predictor
        logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
        rhat[i,k] <- p[i,k] * n[i,k]
#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]])
     }
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) }


# 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 8 Braun 2002, infliximab

Examination	randomised controlled multicentre trial
Number of patients	70
Inclusion criteria	- fulfilled modified New York criteria for ankylosing spondylitis - had severe active disease that was defined by a Bath ankylosing spondylitis disease activity index (BASDAI) of 4 or greater, and spinal pain of 4 or greater on a 10-cm visual analogue scale
Exclusion criteria	- had active tuberculosis within the previous 3 years, specific changes in the radiograph of the chest at baseline, serious infections within the previous 2 months - history of lymphoproliferative disease or other malignant diseases in the past 5 years - had signs or symptoms of severe renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease
Therapy	- intravenous infliximab (5 mg/kg) at week 0, 2 and 6 - placebo at weeks 0, 2, and 6
Co-therapies	DMARDs and oral corticosteroids were withdrawn min. 4 weeks before screening, patients were allowed to take NSAIDs, but the dose could not be increased over the baseline value (the dose could be reduced and such reductions were recorded)
Follow-up time	12 week
Primary endpoint	improvement of disease activity by 50% between baseline and week 12, measured by BASDAI
Secondary endpoints	- improvements in visual analogue score for spinal pain, BASFI, BASMI, SF36, the working group response criteria, concentration of C-reactive protein in serum, and erythrocyte sedimentation rate
JADAD score	5

Table 9 Gorman 2002, etanercept

Examination	a randomized, double-blind, placebo-controlled trial
Number of patients	40
Inclusion criteria	- had to meet the modified New York clinical criteria for definite ankylosing spondylitis - have evidence of active spondylitis despite accepted treatments, and be at least 18 years old - active spondylitis was defined as the presence of inflammatory back pain (stiffness and pain that worsened with rest and improved with exercise), morning stiffness for at least 45 minutes, and at least moderate disease activity as assessed by the patient and the physician
Exclusion criteria	- had a spondylitis other than ankylosing spondylitis, clinical or radiographic evidence of complete spinal ankylosis - a history of recurrent infections or cancer, or a serious liver, renal, hematologic, or neurologic disorder
Therapy	- twice-weekly subcutaneous injections of etanercept (25 mg) for four months - placebo for four months
Co-therapies	Px continued previous Rx regimens (of NSAIDs and/or DMARDS: prednisone, SSZ, MTX, azathioprine, gold)
Follow-up time	4 months
Primary endpoint	20 percent or greater improvement in at least three of five measures of disease activity, as recommended by the Assessments in Ankylosing Spondylitis Working Group (duration of morning stiffness, degree of nocturnal spinal pain, the Bath Ankylosing Spondylitis Functional Index, the patient's global assessment of disease activity, and the score for joint swelling), one of which was required to be duration of morning stiffness or degree of nocturnal spinal pain, with no worsening in any of the measures
Secondary endpoints	the physician's global assessment of disease activity, measures of spinal mobility, the scores for enthesitis and peripheral-joint tenderness, the erythrocyte sedimentation rate, and the C-reactive protein level
JADAD score	5

Table 10 Calin 2004, etanercept

Examination	double blind, randomised, placebo controlled study
Number of patients	84
Inclusion criteria	- aged 18–70 years with active AS (AS was diagnosed using the modified New York criteria. Active disease was diagnosed if the patient had an average score >30 for spinal inflammation and a score >30 on at least two of the other three domains)
Exclusion criteria	- had complete ankylosis (fusion) of the spine - previously used TNFa inhibitors, including etanercept - used DMARDs other than hydroxychloroquine, sulfasalazine, or methotrexate within 4 weeks of baseline - used multiple NSAIDs - used > 10 mg prednisone daily - or changed doses of NSAIDs or prednisone within 2 weeks of baseline
Therapy	- 25 mg injections of etanercept twice weekly for 12 weeks - placebo twice weekly for 12 weeks
Co-therapies	Physiotherapy (where existing programmes, continued); concomitant use of NSAIDs, DMARDs, corticosteriods permitted (participants stratified by baseline DMARD use and then randomised, changes in or multiple NSAID use exclusion criteria
Follow-up time	12 week
Primary endpoint	an improvement of at least 20% in patient reported symptoms, based on the multicomponent Assessments in Ankylosing Spondylitis (ASAS) response criteria (ASAS 20)
Secondary endpoints	ASAS 50 and ASAS 70 responses and improved scores on individual components of ASAS, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), acute phase reactants, and spinal mobility tests
JADAD score	5

Table 11 Davis 2003, etanercept

Examination	multicenter, randomized, placebocontrolled, double-blind trial
Number of patients	277
Inclusion criteria	- men or women ages 18 to 70 years - satisfied the modified New York criteria for AS - had active AS
Exclusion criteria	- had complete ankylosis (fusion) of the spine based on radiographic assessment - had previously received TNF inhibitor therapy - had a serious infection (associated with hospitalization or intravenous antibiotics) within 4 weeks before screening, or were pregnant
Therapy	- etanercept 25 mg subcutaneously twice weekly for 24 weeks - placebo subcutaneously twice weekly for 24 weeks
Co-therapies	Px continued stable Rx regimens of HCQ, SSZ, MTX, NSAIDs or prednisone; standard doses of analgesics (paracetamol, codeine, hydrocodone, oxycodone, tramadol) permitted
Follow-up time	24 week
Primary endpoint	the percentages of patients achieving the Assessments in Ankylosing Spondylitis 20% response (ASAS20) at weeks 12 and 24
Secondary endpoints	achievement of the ASAS50 and ASAS70
JADAD score	5

Table 12 Heijde 2005, ASSERT, infliximab

Examination	multicenter, randomized, placebo-controlled study
Number of patients	279
Inclusion criteria	- having AS (according to the modified New York criteria) for at least 3 months prior to screening, with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4 (range 0–10), and with a spinal pain assessment score of ≥ 4 on a visual analog scale (VAS; range 0–10 cm) - have a normal chest radiograph within 3 months prior to randomization and either a negative purified protein derivative (PPD) skin test result for latent tuberculosis (in the US and Canada) or adequate screening with documented negative results for latent tuberculosis using local guidelines for high-risk or immunocompromised patients (in Europe)
Exclusion criteria	- had any of the following diagnoses or medical history: total ankylosis of the spine (defined by syndesmophytes present on the lateral views of spinal radiographs at all intervertebral levels from T6 through S1), any other inflammatory rheumatic disease, fibromyalgia, a serious infection within 2 months prior to randomization, tuberculosis (active or latent) or recent contact with a person with active tuberculosis, an opportunistic infection within 6 months of screening, hepatitis, human immunodeficiency virus, a transplanted organ, malignancy, multiple sclerosis, or congestive heart failure - receive sulfasalazine or methotrexate within 2 weeks prior to screening, systemic corticosteroids within 1 month prior to screening, anti-TNF therapy other than infliximab within 3 months prior to screening, infliximab at any time prior to screening, DMARDs other than sulfasalazine or methotrexate within 6 months prior to screening, or cytotoxic drugs within 12 months prior to screening
Therapy	infusions of placebo at weeks 0, 2, 6, 12, and 18 infusions of 5 mg/kg infliximab at weeks 0, 2, 6, 12, and 18
Co-therapies	Permitted: NSAIDs (paracetamol, tramadol) stable doses; not permitted: SSZ, MTX <2 weeks*, DMARDs (other than SSZ or MTX) <6 months*, systemic corticosteroids <1 month, anti-TNF (other than infliximab) <3 months*, cytotoxic drugs <12 months* (*prior to screening)
Follow-up time	24 week
Primary endpoint	the proportion of patients with a 20% improvement response according to the ASAS International Working Group criteria (ASAS20 responders) at week 24
Secondary endpoints	- ASAS40 response (40% improvement from baseline and an absolute improvement of at least 2 units [on a scale of 0–10] in at least 3 of the 4 assessment domains defined in the ASAS20 response criteria, with no deterioration from baseline in the potential remaining assessment domain) - ASAS partial remission (an absolute score of <2 in each of the above 4 ASAS assessment domains), and 20% improvement in at least 5 of the following 6 ASAS assessment domains (an ASAS 5 of 6 response): spinal pain, patient's global assessment, function according to the BASFI, morning stiffness, CRP level, and the Bath Ankylosing Spondylitis Metrology Index (BASMI) score - disease activity, physical function, range-of-motion assessments, other musculoskeletal assessments, and quality of life
JADAD score	5

Table 13 Heijde, 2006, adalimumab ATLAS

Examination	multicenter, randomized, double-blind, placebo-controlled study
Number of patients	315
Inclusion criteria	- at least 18 years of age and were classified as having definite AS based on the modified New York criteria - had active disease, which was defined as fulfillment of at least 2 of the following 3 criteria: a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4, a total back pain score ≥ 4 by visual analog scale (VAS; 0–10 cm), or a duration of morning stiffness ≥ 1 hour - patients with stable and well-controlled psoriasis, uveitis, inflammatory bowel disease (i.e., ulcerative colitis, Crohn's disease), and reactive arthritis - inadequate response or intolerance to 1 or more nonsteroidal antiinflammatory drugs (NSAIDs)
Exclusion criteria	- had previously received anti-TNF therapy, cyclosporine, azathioprine, or DMARDs (other than the medications and dosages listed above) at any time and patients who had received intraarticular injection(s) with corticosteroids within 4 weeks prior to baseline - clinically active TB were - a history of any recent infections requiring antibiotic treatment; hepatitis or human immunodeficiency virus; a significant history of cardiac, renal, neurologic, psychiatric, endocrinologic, metabolic, or hepatic disease; and a history of demyelinating disease or multiple sclerosis - a history of cancer or lymphoproliferative disease other than a successfully treated nonmetastatic squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix
Therapy	- subcutaneous injection of adalimumab, 40 mg every other week - placebo for 24 weeks
Co-therapies	DMARDs (corticosteroids, MTX, SSZ or HCQ) should not have been initiated or increased before week 36; corticosteroids, could have been decreased, or stopped after week 24 at investigator's discretion. MTX, SSZ or HCQ should not have been decreased before week 36
Follow-up time	24 week
Primary endpoint	the percentage of patients with a 20% response according to the ASsessment in Ankylosing Spondylitis International Working Group criteria for improvement (ASAS20) at week 12
Secondary endpoints	ASAS20 at week 24 and multiple measures of disease activity, spinal mobility, and function, as well as ASAS partial remission
JADAD score	5

Table 14 Maksymowich 2005 Canadian AS, Lambert, 2007, adalimumab

Examination	multicenter, randomized, double-blind, placebo-controlled study
Number of patients	82
Inclusion criteria	- adults (≥ 18 years of age) diagnosed as having AS as defined by the modified New York criteria - had been treated unsuccessfully (nonresponse or lack of tolerance) with ≥ 1 nonsteroidal antiinflammatory drugs (NSAIDs) - had failed to respond to ≥ 1 disease-modifying antirheumatic drugs (e.g., methotrexate, sulfasalazine) - active AS at baseline was defined by fulfillment of 2 of the following 3 criteria: a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI score ≥ 4, total back pain visual analog scale score ≥ 40, or morning stiffness of ≥ 1 hour in duration
Exclusion criteria	-
Therapy	- 40 mg adalimumab every other week during the initial 24-week double-blind period - placebo every other week during the initial 24-week double-blind period
Co-therapies	DMARDs (corticosteroids, MTX, SSZ or HCQ) should not have been initiated or increased before week 36; corticosteroids, could have been decreased, or stopped after week 24 at investigator's discretion. MTX, SSZ or HCQ should not have been decreased before week 36
Follow-up time	24 week
Primary endpoint	ASAS20 response at week 12
Secondary endpoints	SPARCC scores
JADAD score	4

Table 15 Heijde 2006, etanercept

Examination	randomised, double-blind, placebocontrolled, multicentre study
Number of patients	356
Inclusion criteria	- aged 18–70 years, with active ankylosing spondylitis based on the Modified New York Criteria for ankylosing spondylitis - active ankylosing spondylitis was defined by an average visual analogue scale (VAS) score ≥ 30 for duration and intensity of morning stiffness and two or more of the following: patient global assessment of disease activity VAS score ≥ 30; mean of nocturnal and total pain VAS scores ≥ 30; or Bath Ankylosing Spondylitis Functional Index ≥ 30 (all scores on a scale of 0-100)
Exclusion criteria	- previously treated with TNFa inhibitors, including etanercept or other biological agents, or disease-modifying antirheumatic drugs (other than hydrochloroquine, sulfasalazine and methotrexate) less than 4 weeks before baseline - complete ankylosis (fusion) of the spine based on radiographic assessment and concurrent medical events, such as uncontrolled hypertension, unstable angina pectoris, congestive heart failure, severe pulmonary disease, cancer, demyelinating diseases of the central nervous system and serious infections
Therapy	- etanercept 50 mg once weekly - etanercept 25 mg twice weekly - placebo
Co-therapies	
Follow-up time	12 week
Primary endpoint	the proportion of patients achieving a response at week 12 based on the Assessment in Ankylosing Spondylitis Working Group criteria (ASAS 20)
Secondary endpoints	- the proportion of responders based on ASAS 40 and ASAS 5/6 criteria at all time points - ASAS 40 is based on the same domains as ASAS 20, but requires at least a 40% improvement and 20 units in at least three of the four domains and no worsening in the remaining domain.20 ASAS 5/6 responders are defined as patients showing >20% improvement in five of six domains: the four domains in ASAS 20 and C reactive protein (CRP) levels, and spinal mobility (modified Schober's test) patient and physician global assessments of disease activity, nocturnal and total back pain assessments, Bath Ankylosing Spondylitis Functional Index, Bath Ankylosing Spondylitis Disease Activities Index (BASDAI), patients achieving partial remission, time to partial remission, spinal mobility (modified Schober's test, chest expansion measurement and occiput-to-wall distance), joint assessment (70 joints) and serum CRP
JADAD score	4

Table 16. Barkham 2010, etanercept

Examination	randomised double-blind placebo-controlled study
Number of patients	40
Inclusion criteria	- had a definite diagnosis of AS by modified New York Criteria and active disease as defined by two out of three of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥40 (0–100), visual analogue scale (VAS) pain ≥40 (0–100), early morning stiffness ≥45 min - all were in work but were work unstable (AS-WIS score >10)
Exclusion criteria	past or current tuberculosis, congestive heart disease or treatment with glucocorticoids in the previous month
Therapy	- 25 mg etanercept twice weekly for 12 weeks - placebo twice weekly for 12 weeks
Co-therapies	-
Follow-up time	12 week
Primary endpoint	- change in AS-WIS at week 12
Secondary endpoints	- clinical outcomes and gait parameters: assessments of disease activity (BASDAI), quality of life, functional ability (Bath Ankylosing Spondylitis Functional Index (BASFI), gait parameters using an electronic walkway and disability (Disability Index of Stanford Health Assessment Questionnaire (HAQ-DI)
JADAD score	4

Table 17. Doudogas 2011, SPINE study, etanercept

Examination	multicentre randomised double-blind placebo-controlled trial
Number of patients	82
Inclusion criteria	- men and women aged 18–70 years were eligible if they had a current diagnosis of AS as defined by the modified New York criteria - patients also had to have baseline pain with axial involvement of the overall level of AS neck, back or hip for a score ≥30 on a 0–100 mm visual analogue scale - had to have an active refractory disease defined by a score ≥40 on the Bath AS Disease Activity Index (BASDAI) (0–100) despite optimal non-steroidal anti-inflammatory drug (NSAID) treatment (at least two NSAIDs at the maximal tolerated dose for >3 months and according to the opinion of the investigator)
Exclusion criteria	- had been previously exposed to a TNF inhibitor, if the NSAID dose had changed within 2 weeks of baseline evaluation and if the dose of concomitant conventional disease-modifying antirheumatic drug, if taken, had changed within 4 weeks of baseline evaluation - had significant concurrent medical disorders (eg, cancer or history of cancer, serious infection) and/or abnormal laboratory test results
Therapy	- ETN 50 mg once weekly - placebo
Co-therapies	- during the 12 weeks of the study the dose of concomitant NSAIDs and any concomitant DMARD had to remain stable - in case of a painful episode during the study, analgesics such as paracetamol, with or without codeine or dextropropoxyphen, could be used
Follow-up time	12 week
Primary endpoint	- BASDAI between randomisation and week 12
Secondary endpoints	- ASAS20, ASAS40, ASAS5/6, ASAS partial remission, and improvement in BASDAI of at least 50% (BASDAI50), improvement in AS-DAS and AS-DAS status
JADAD score	5

Table 18. Inman, 2008, GO-RAISE, golimumab

Examination	randomized, double-blind, placebo-controlled, phase III trial
Number of patients	356
Inclusion criteria	- had AS, a spinal pain assessment score of ≥ 4 on a visual analog scale (VAS; 0–10-cm scale), and an inadequate response to current or previous nonsteroidal antiinflammatory drugs (NSAIDs) or disease-modifying antirheumatic drugs - normal results of a chest radiograph within 3 months before randomization and to have undergone screening for latent tuberculosis (TB) using a purified protein derivative skin test and the QuantiFERON TB Gold test - patients who were receiving NSAIDs had to have received continuous therapy for 3 months at the highest recommended doses or had to have been unable to receive a full 3-month course of full-dose NSAID therapy because of intolerance, toxicity, or contraindications - patients in whom latent TB was discovered were required to initiate therapy for TB prior to or simultaneously with the first dose of the study agent
Exclusion criteria	- had any of the following: complete ankylosis of the spine, any other inflammatory rheumatic disease, a serious infection within 2 months before randomization, active or latent TB or positive results of a tuberculin skin test before screening or recent contact with a person with active TB, an opportunistic infection within 6 months of screening, hepatitis, human immunodeficiency virus, a transplanted organ, malignancy, multiple sclerosis, or congestive heart failure
Therapy	- golimumab 50 mg - golimumab 100 mg - placebo
Co-therapies	- patients were allowed to continue concurrent treatment with methotrexate (MTX), sulfasalazine, hydroxychloroquine, corticosteroids, and NSAIDs at stable doses during the study
Follow-up time	24 week
Primary endpoint	proportion of patients with at least 20% improvement in the ASsessment in AS (ASAS20) criteria at week 14
Secondary endpoints	- ASAS 40% improvement (ASAS40), ASAS partial remission, and 20% improvement in 5 of 6 ASAS domains (ASAS5/6)
JADAD score	5

Table 19. Huang 2013, adalimumab

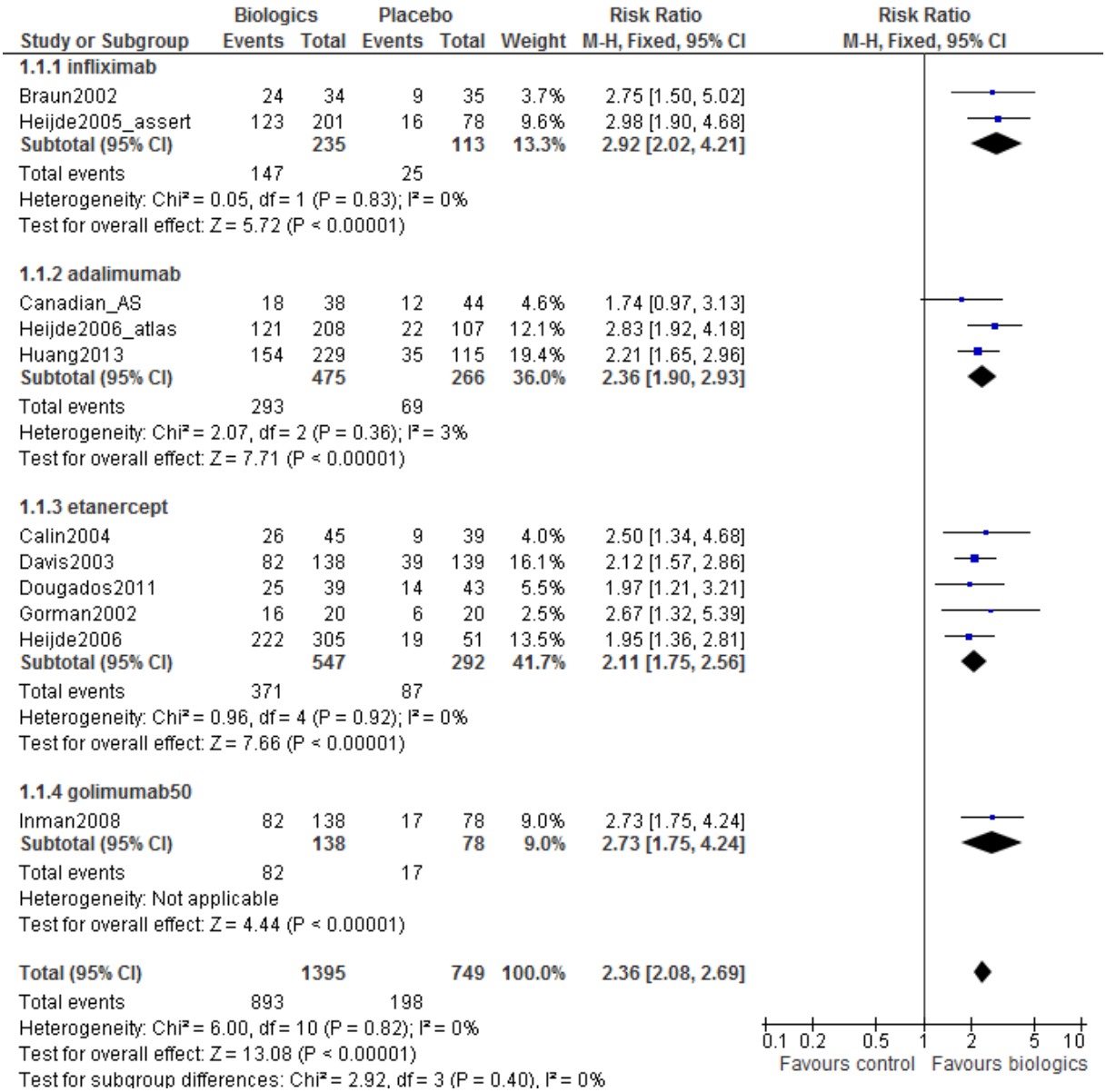
Examination	placebo-controlled, double-blind, randomised, phase III trial
Number of patients	344
Inclusion criteria	- 18 and 65 years of age, fulfilled modified New York Criteria for AS, had active disease (as defined by ≥2 of the following: Bath AS Disease Activity Index (BASDAI) ≥4 cm; total back pain on a visual analogue scale (VAS) ≥4 cm; and ≥1 hour of morning stiffness), and had an inadequate response or were intolerant to ≥1 NSAID
Exclusion criteria	- patients with latent tuberculosis (TB) based on results of a positive purified protein derivative (PPD) test and chest radiograph had either completed or were receiving anti-TB therapy; patients with active, untreated TB - if they had total spinal ankylosis (bamboo spine); unstable extra-articular manifestations (eg, psoriasis, uveitis, inflammatory bowel disease); surgery involving the spine or joints within the previous 2 months; intra-articular or spinal/paraspinal corticosteroid injections within the previous 28 days; positive serology for HIV antibody, hepatitis B surface antibody or hepatitis C virus antibody; recent infection requiring anti-infectives; listeriosis; histoplasmosis; immunodeficiency syndrome; or chronic recurring infections - moderate to severe congestive heart failure, recent cerebrovascular accident, central nervous system demyelinating disease, or history of malignancy - prior exposure to TNF-α inhibitors, natalizumab or efalizumab at any time, or use of traditional Chinese medicines within 28 days of baseline
Therapy	- adalimumab 40 mg subcutaneously every other week (EOW) for 12 weeks - placebo subcutaneously every other week (EOW) for 12 weeks
Co-therapies	- concomitant use of methotrexate (≤25 mg/week), sulfasalazine (≤3 g/day), prednisone (≤10 mg/day), NSAIDs and/or analgesics was allowed but dose adjustments, induction and/or discontinuation of these therapies were only permitted during the open-label period
Follow-up time	12 week
Primary endpoint	- the percentage of patients meeting the Assessment in Spondyloarthritis International Society (ASAS20) response criteria at week 12
Secondary endpoints	- at weeks 12 and 24 were the percentage of patients achieving the following outcome measures: ASAS40, ASAS5/6, high-sensitivity C-reactive protein (hs-CRP); percentage of patients achieving ASAS partial remission, the percentage of patients achieving at least 50% improvement in the BASDAI score (BASDAI50) - disease activity, pain and spinal mobility by measuring changes from baseline in PTGA (VAS), total back pain (VAS), inflammation/morning stiffness, BASDAI, physician's global assessment of disease activity (VAS), nocturnal pain (VAS), patient's global assessment of pain (VAS), tender joint count, swollen joint count, Maastricht AS Enthesitis Score (MASES), BASMI-linear and chest expansion
JADAD score	5

8.6 Detailed results from classical direct meta-analysis

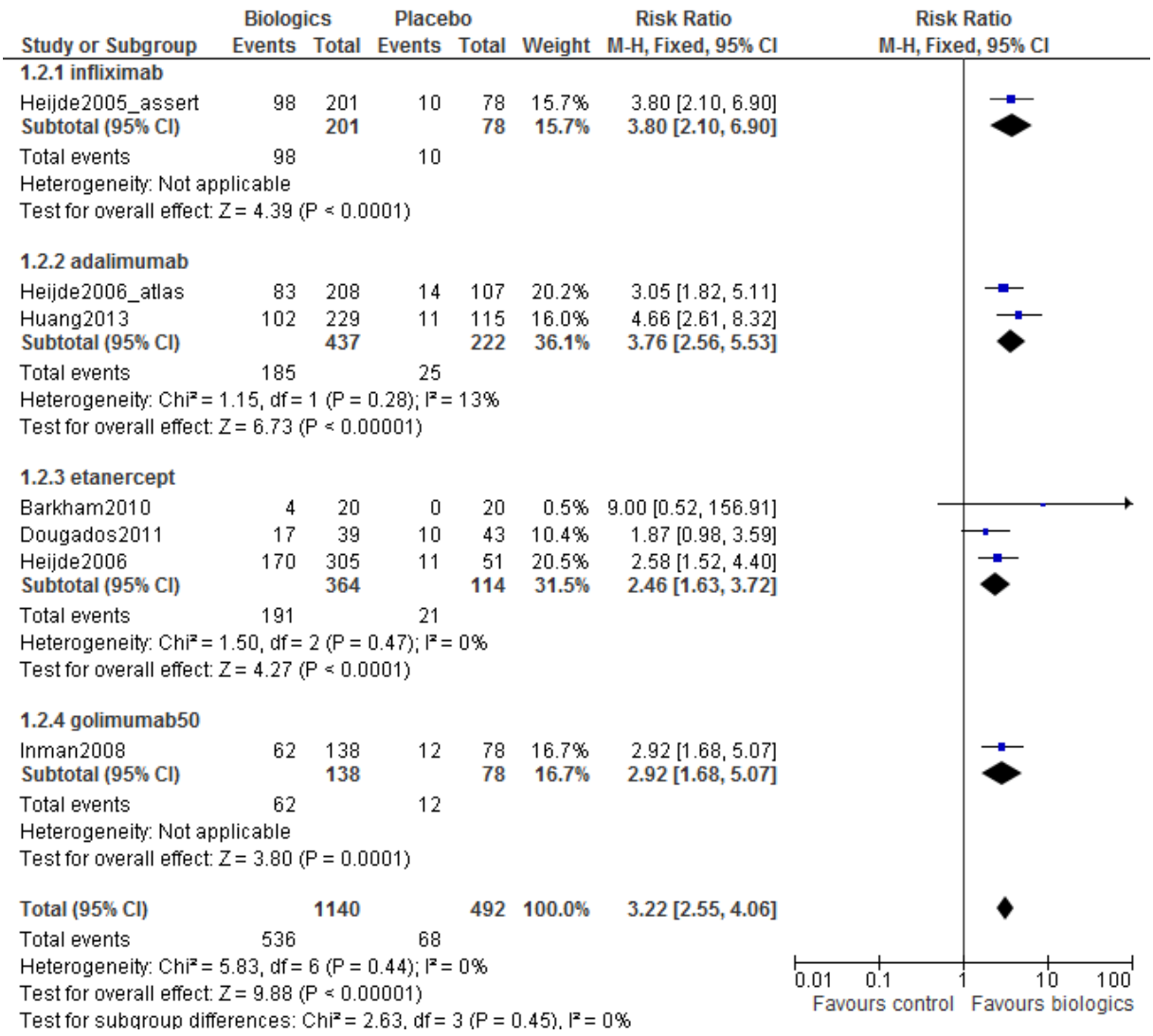
Note: In some of the cases exact numbers were not presented in the studies, only graphs. In the following cases the numbers were read from graphs:

- Braun 2002: ASAS20, ASAS partial remission at week 12
- Heijde 2005 ASSERT: ASAS20, ASAS 40 at week 12
- Heijde 2006 ATLAS: ASAS20 at week 24
- Inman 2008: ASAS40, ASAS5/6, ASAS partial remission at week 12 and 24

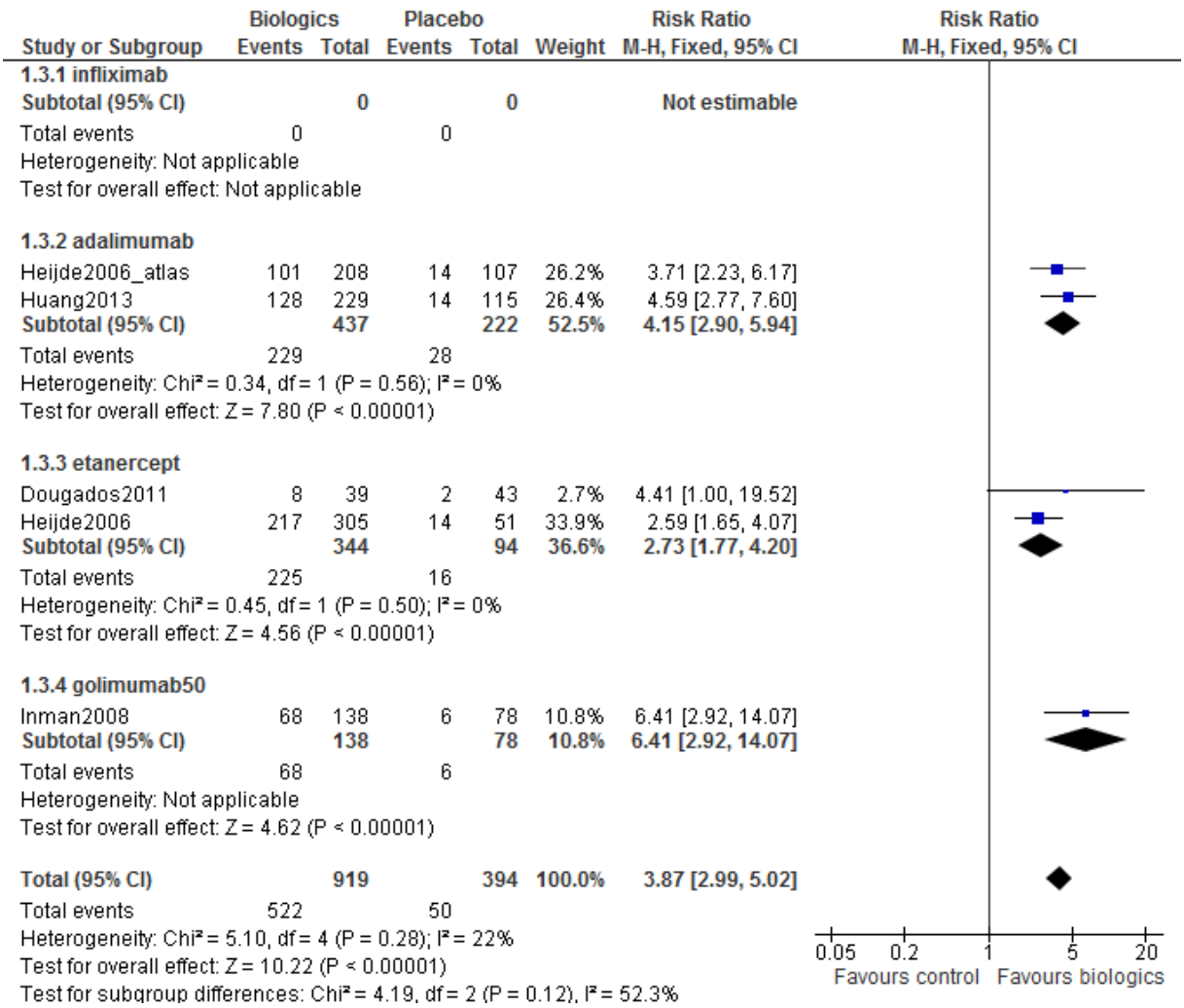
Forest plot of comparison: Efficacy of biologicals – ASAS20 at week 12



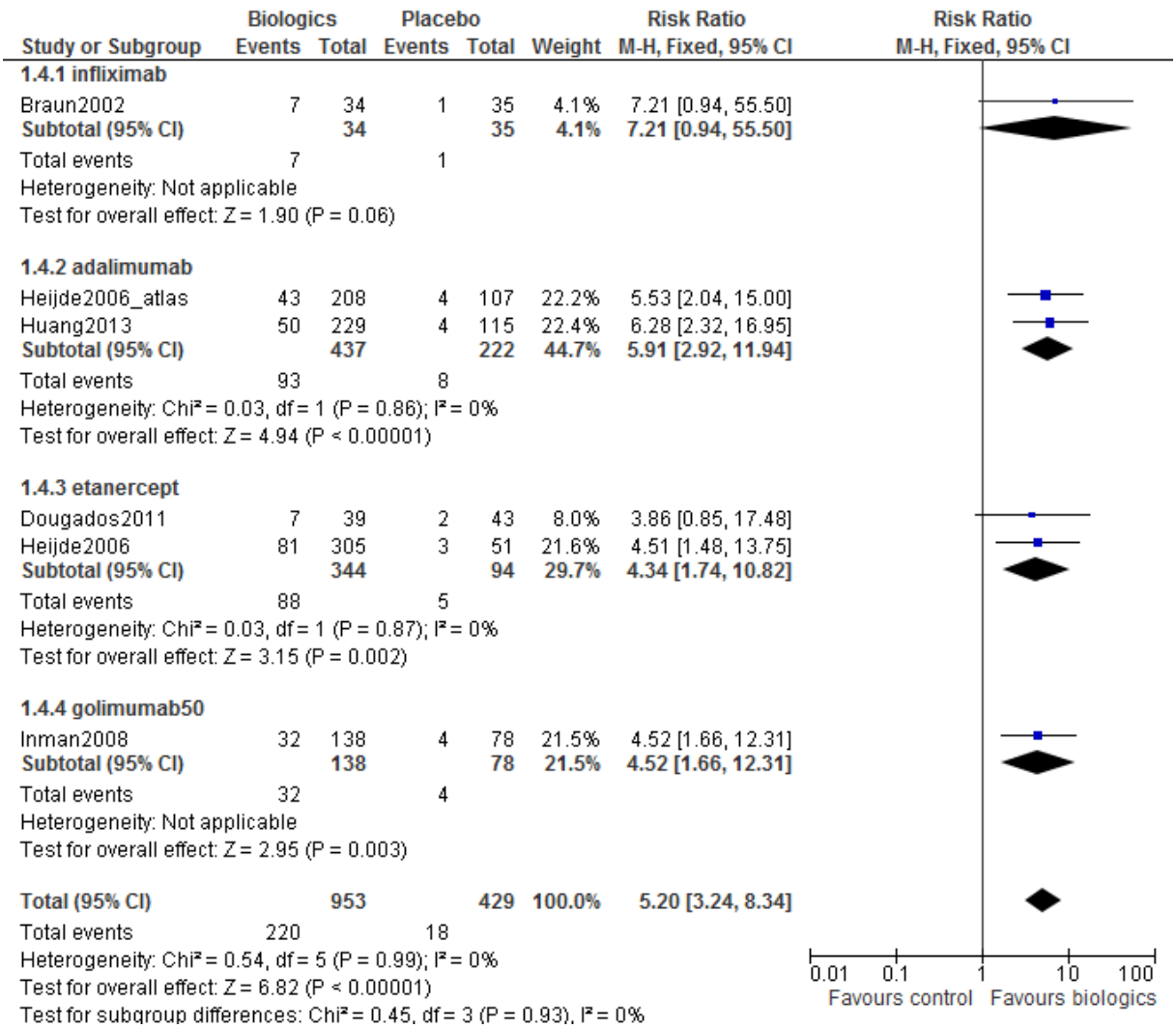
Forest plot of comparison: Efficacy of biologicals – ASAS40 at week 12



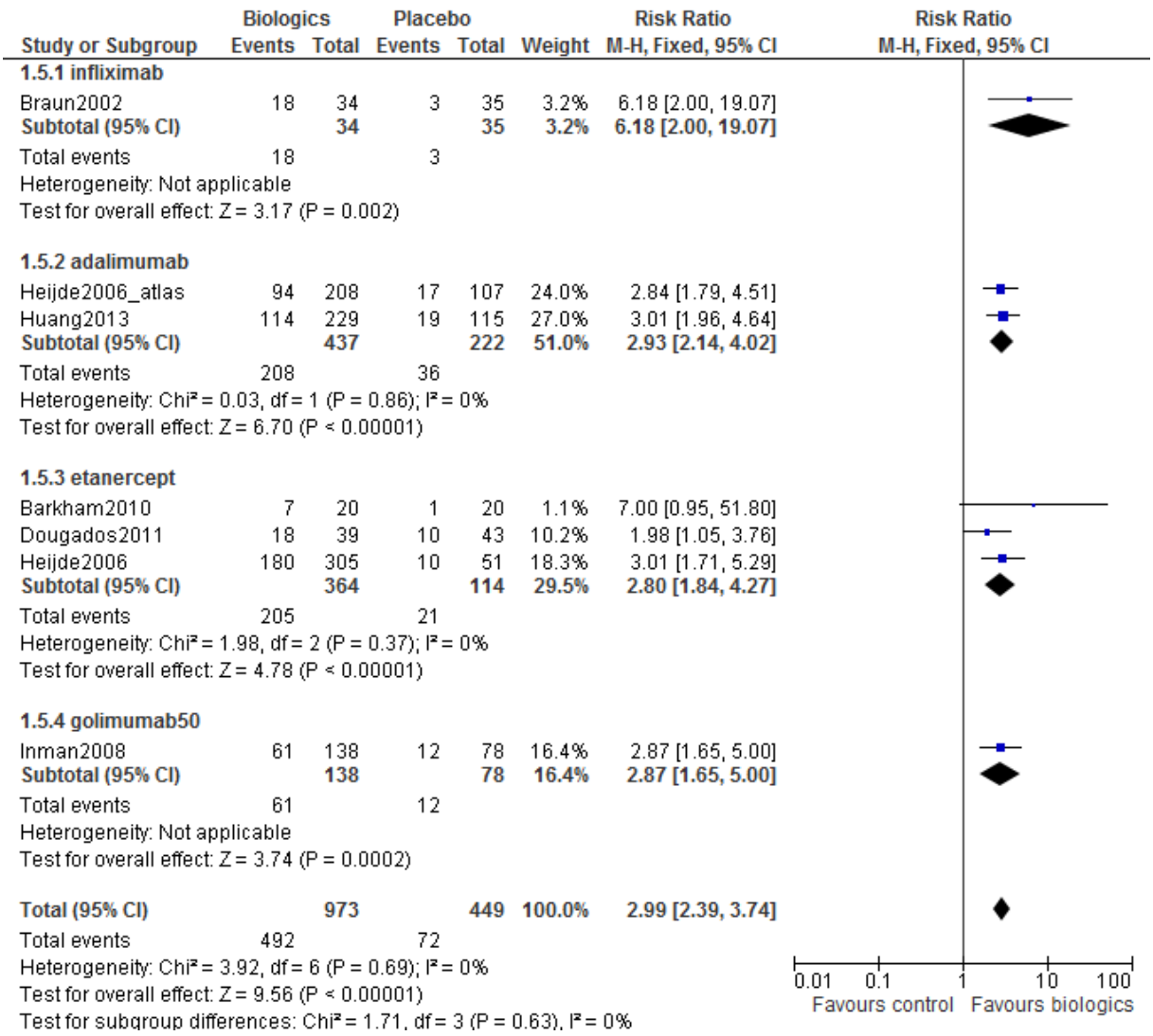
Forest plot of comparison: Efficacy of biologicals – ASAS5/6 at week 12



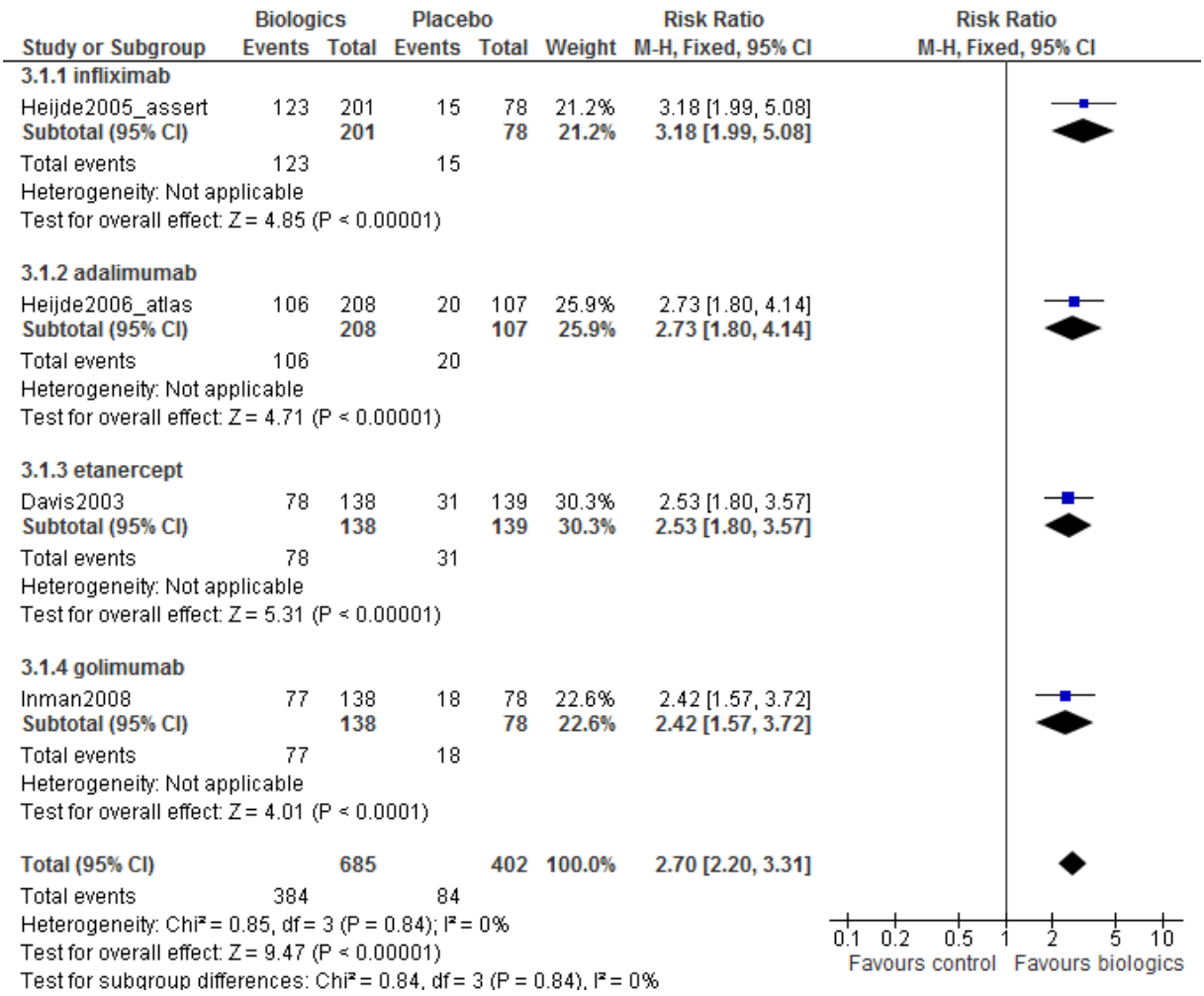
Forest plot of comparison: Efficacy of biologicals – ASAS Partial remission at week 12



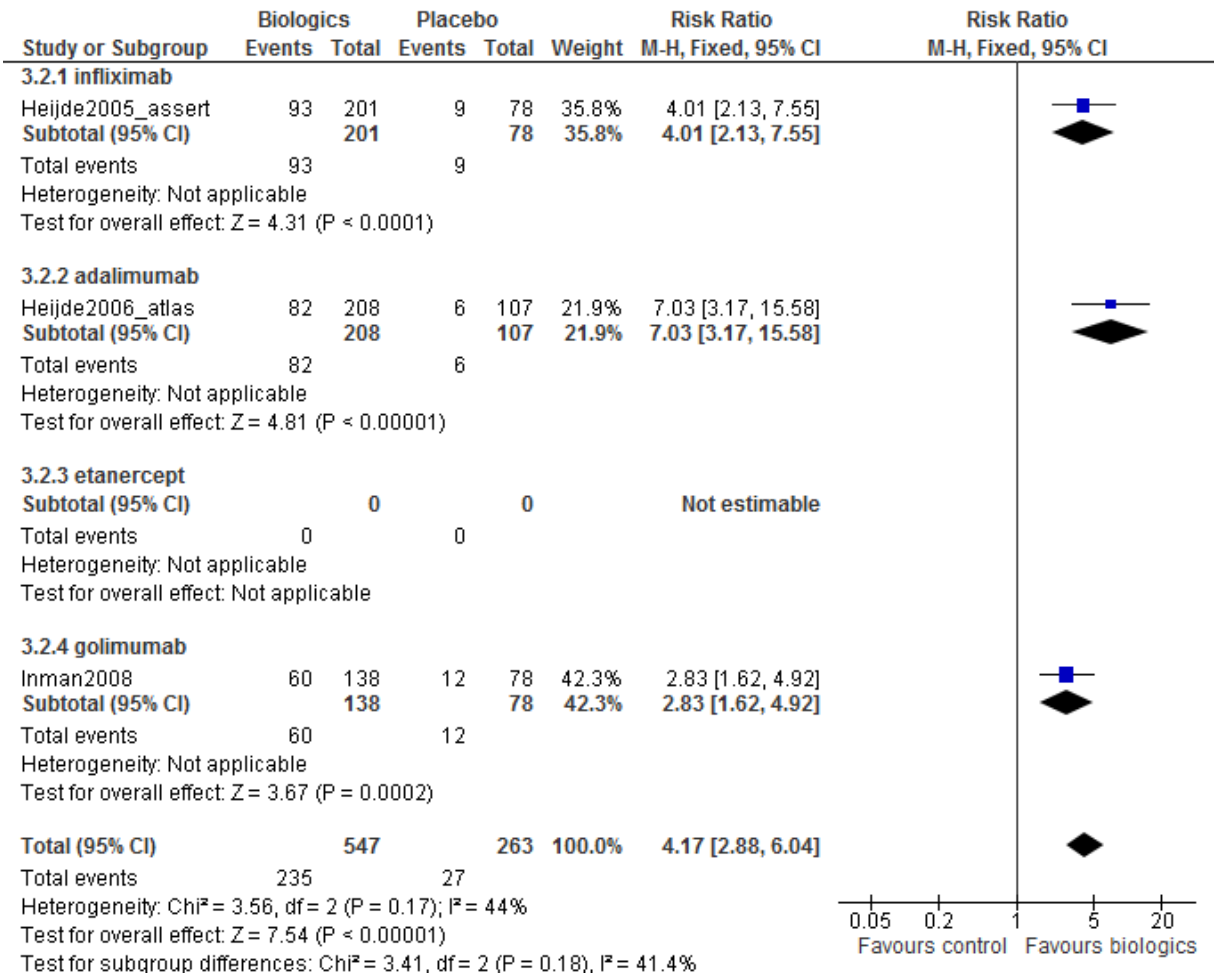
Forest plot of comparison: Efficacy of biologicals – BASDAI 50 at week 12



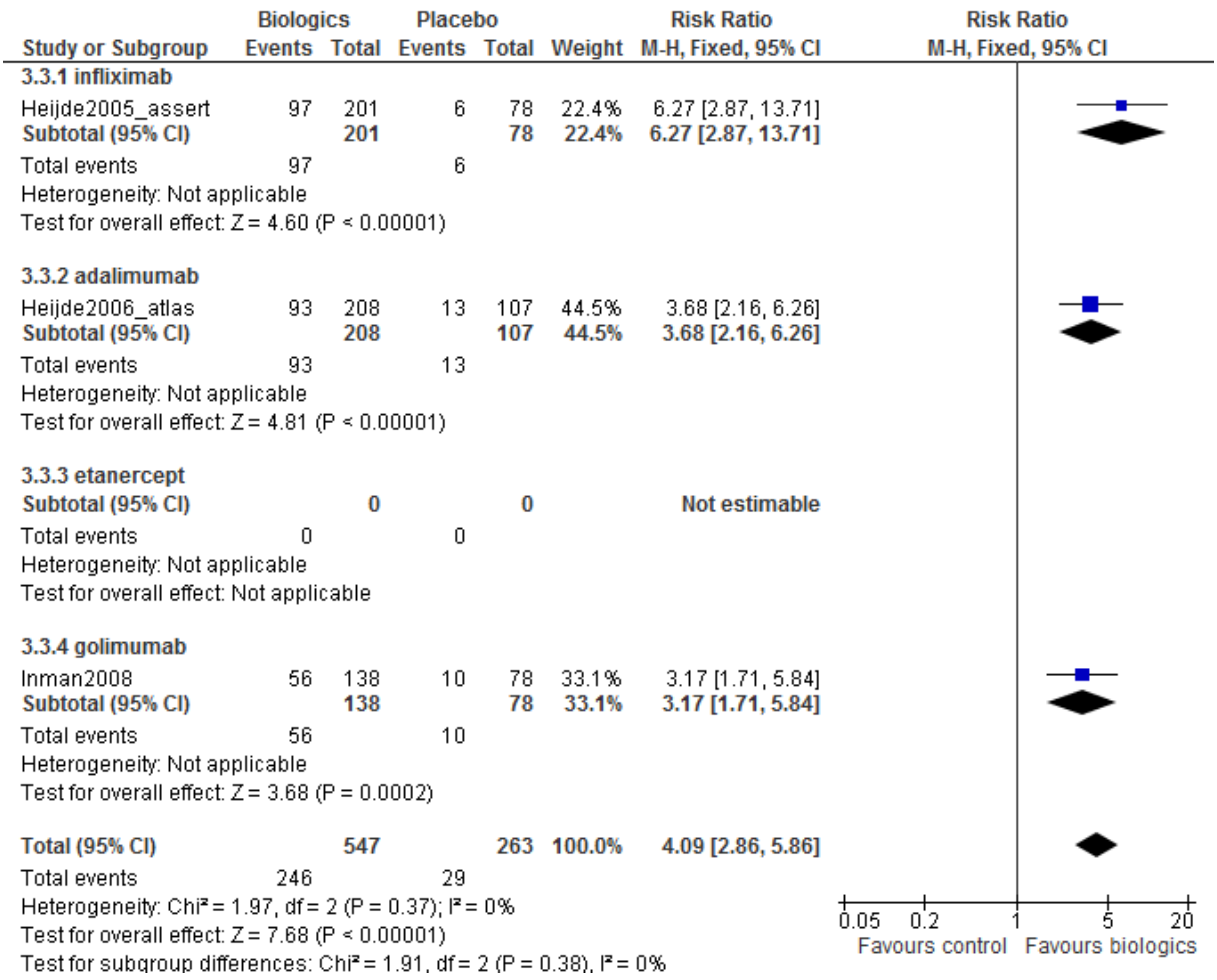
Forest plot of comparison: Efficacy of biologicals – ASAS20 at week 24



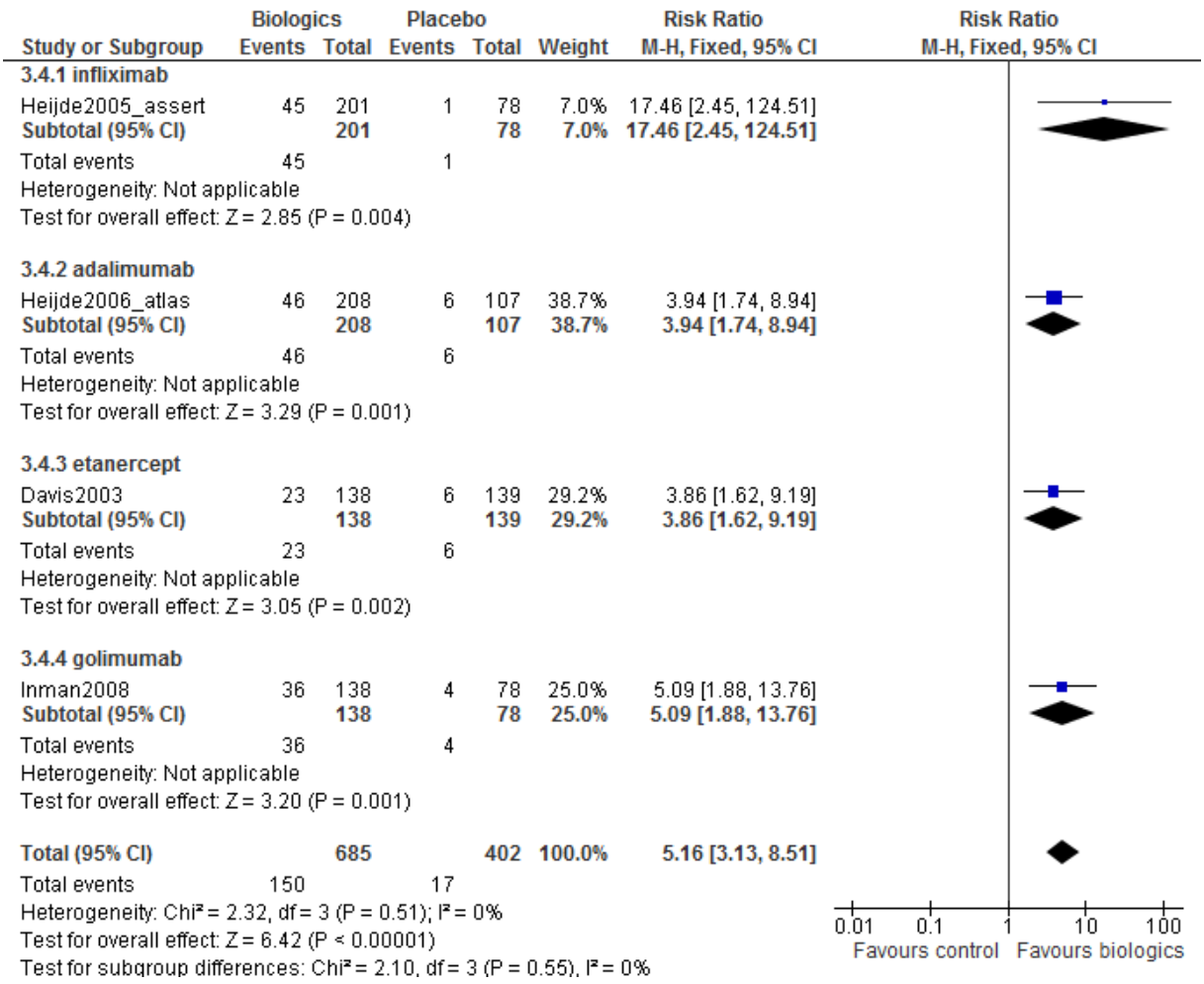
Forest plot of comparison: Efficacy of biologicals – ASAS40 at week 24



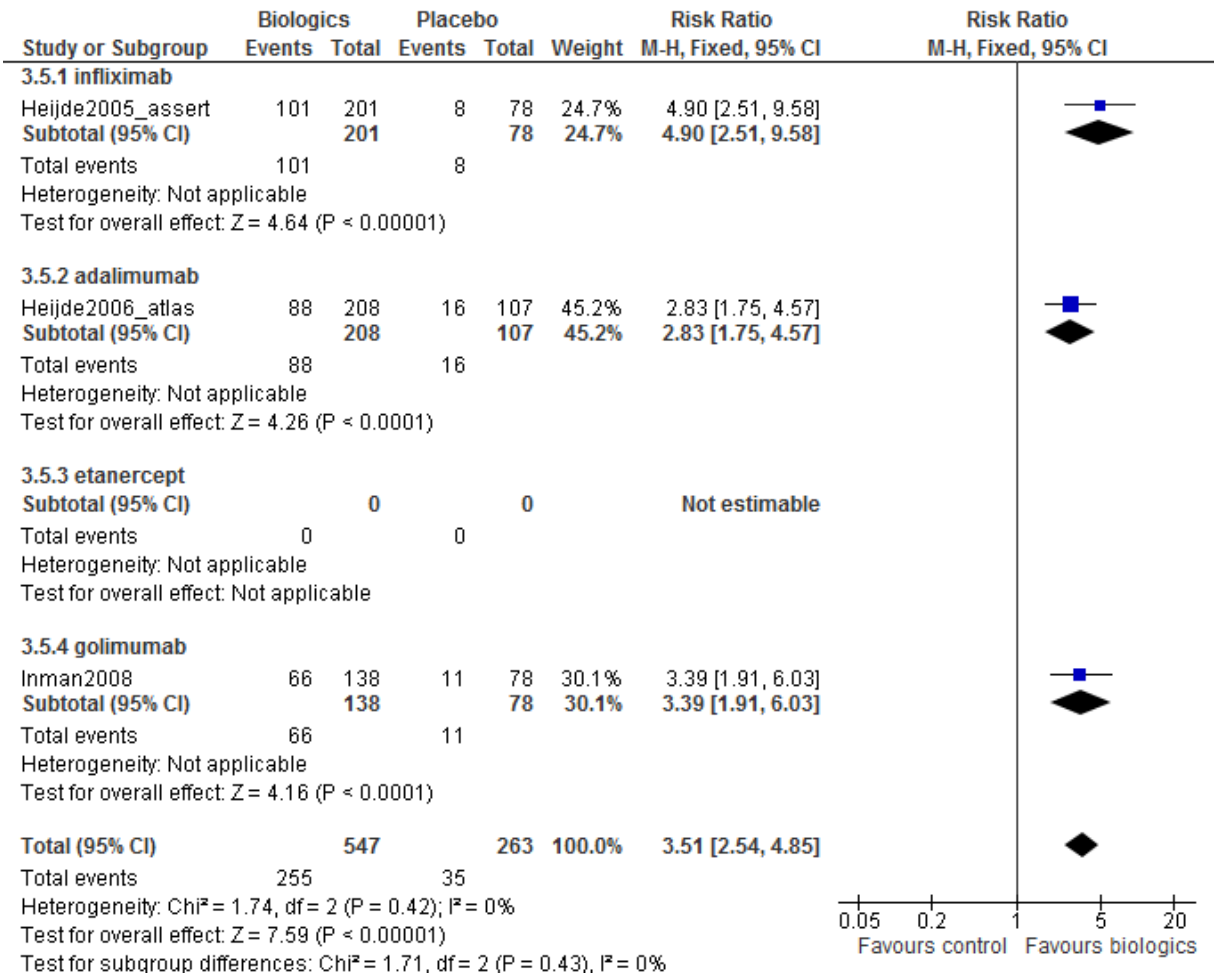
Forest plot of comparison: Efficacy of biologicals – ASAS5/6 at week 24



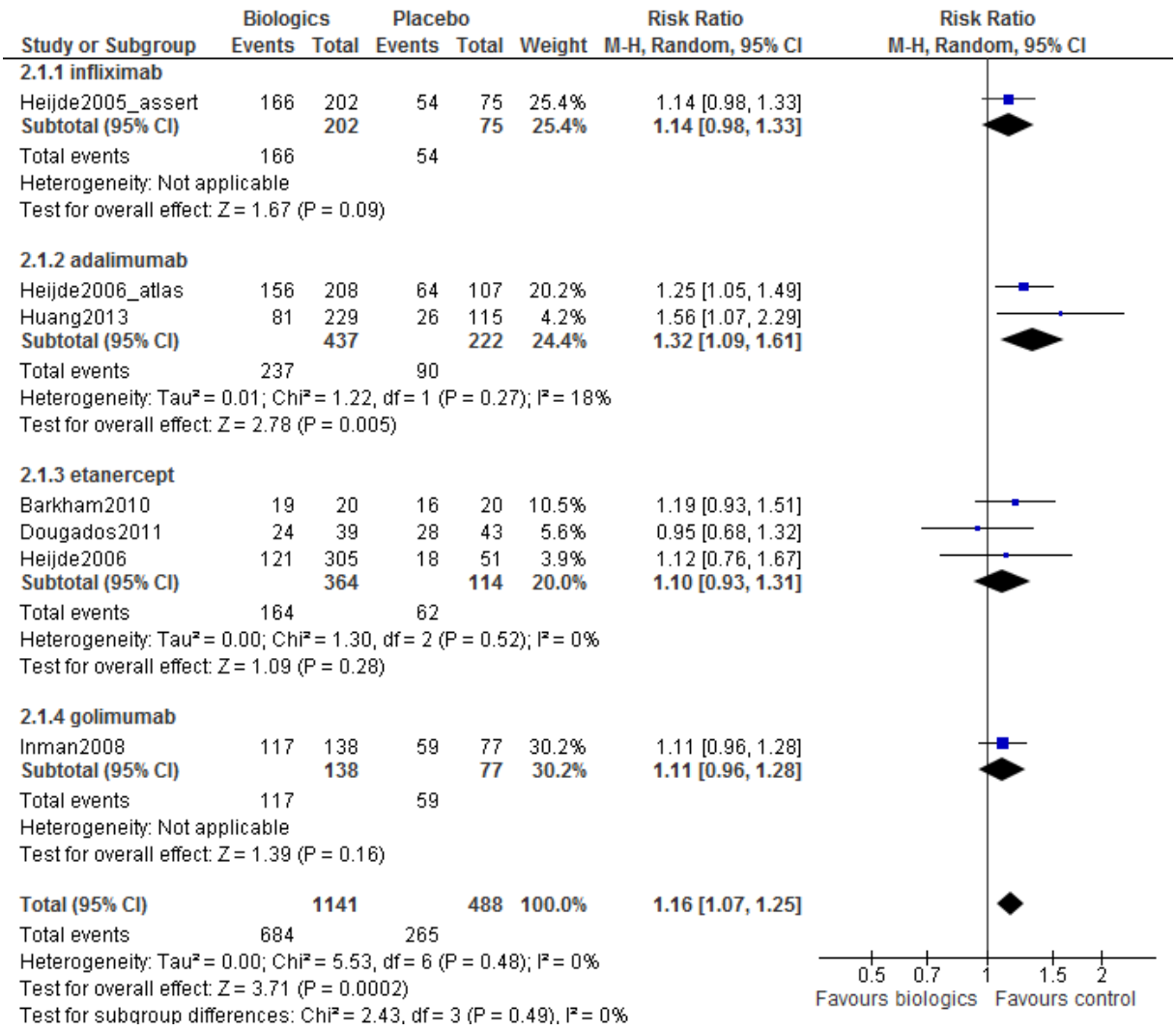
Forest plot of comparison: Efficacy of biologicals – ASAS Partial remission at week 24



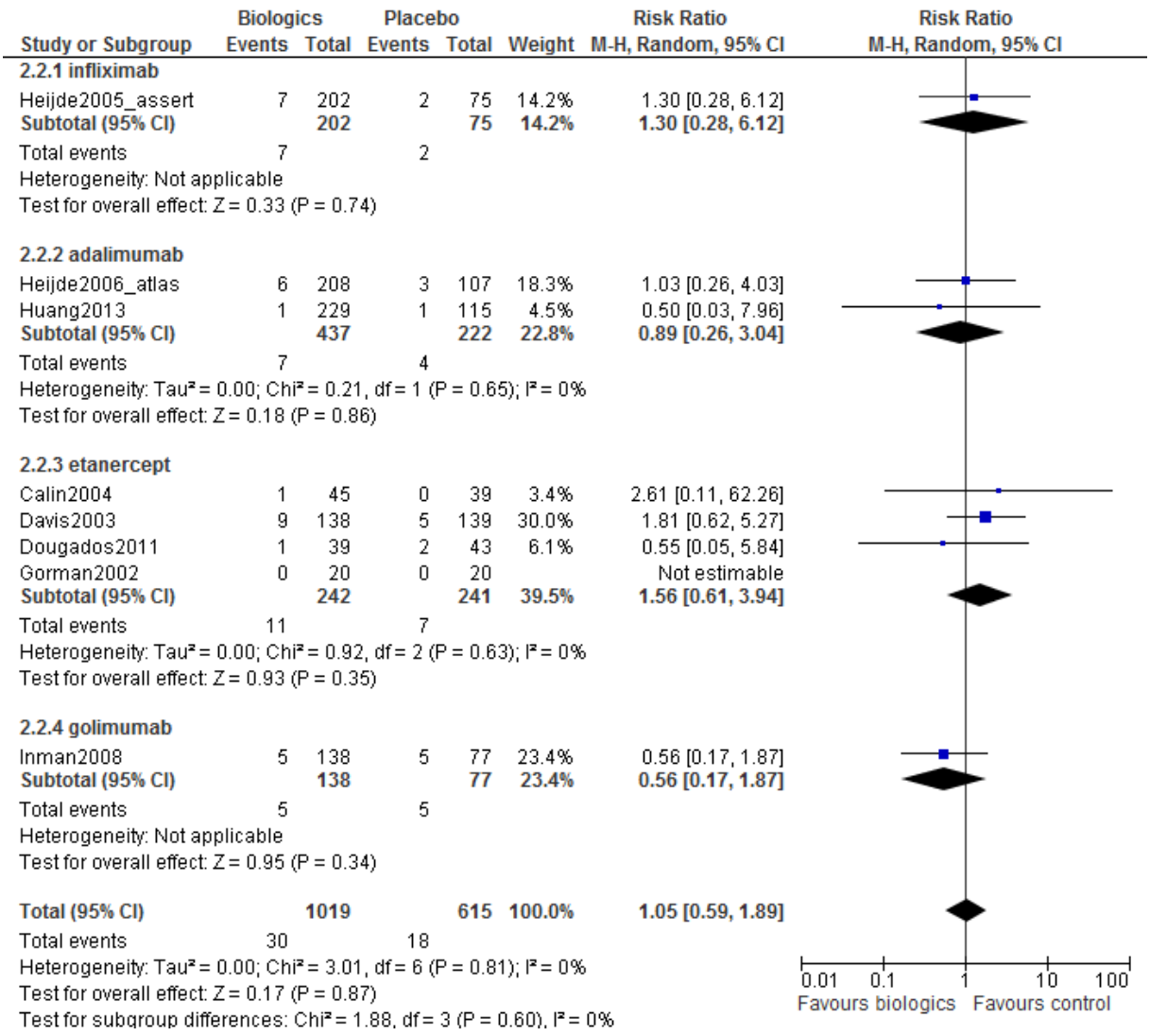
Forest plot of comparison: Efficacy of biologicals – BASDAI 50 at week 24



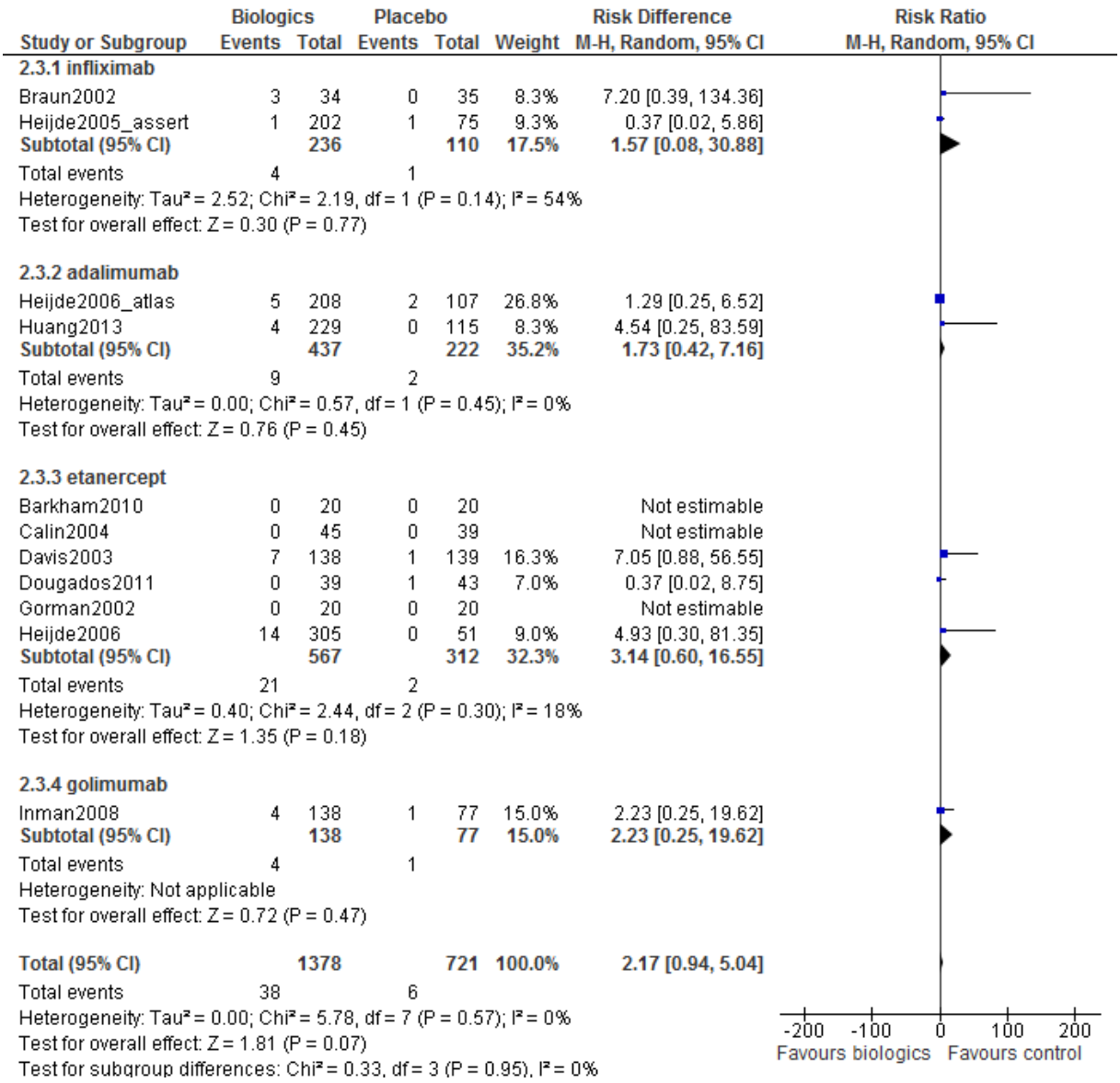
Forest plot of comparison: Safety of biologicals – Adverse events



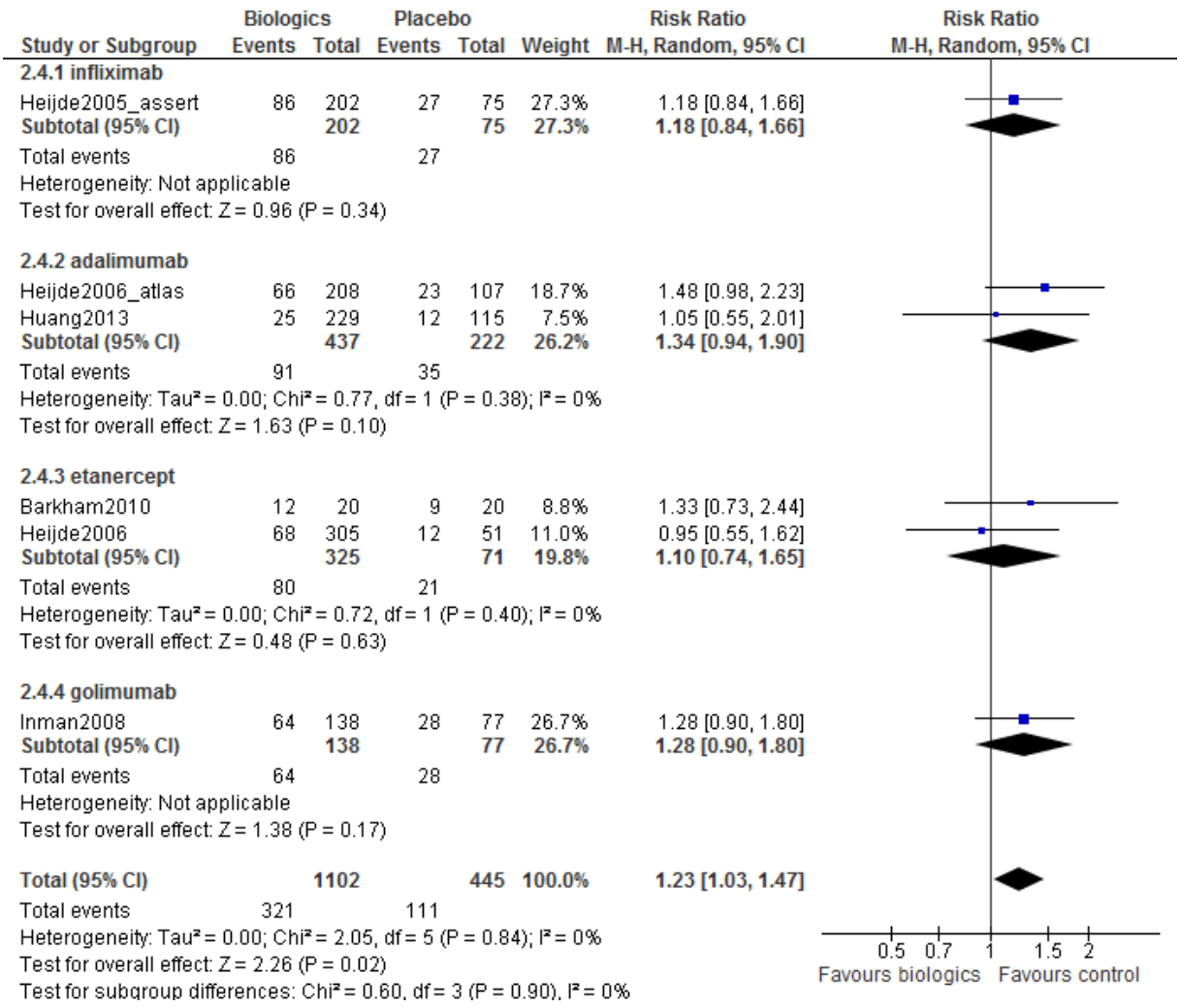
Forest plot of comparison: Safety of biologicals – Serious adverse events



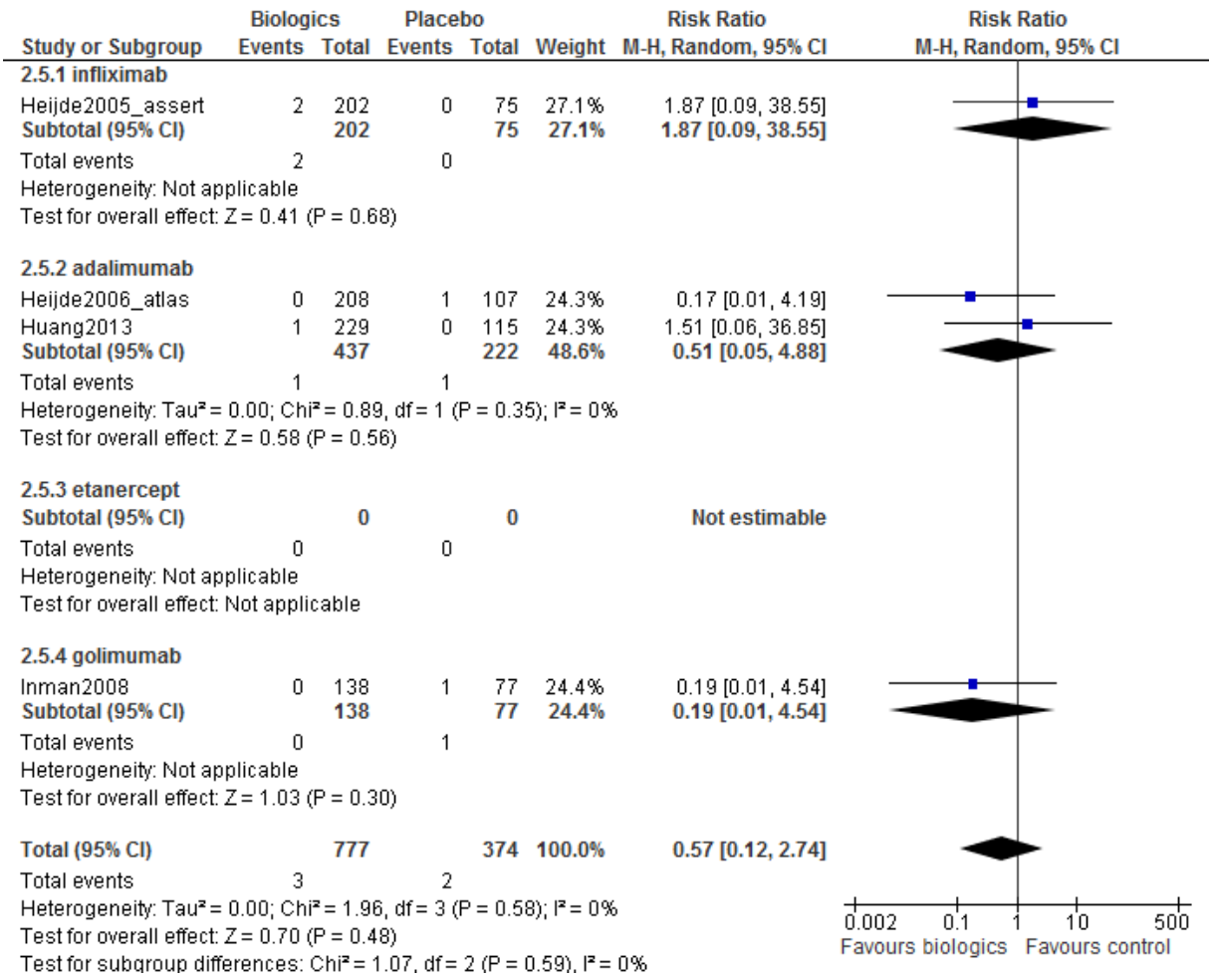
Forest plot of comparison: Safety of biologicals – Adverse events leading to discontionuation of therapy



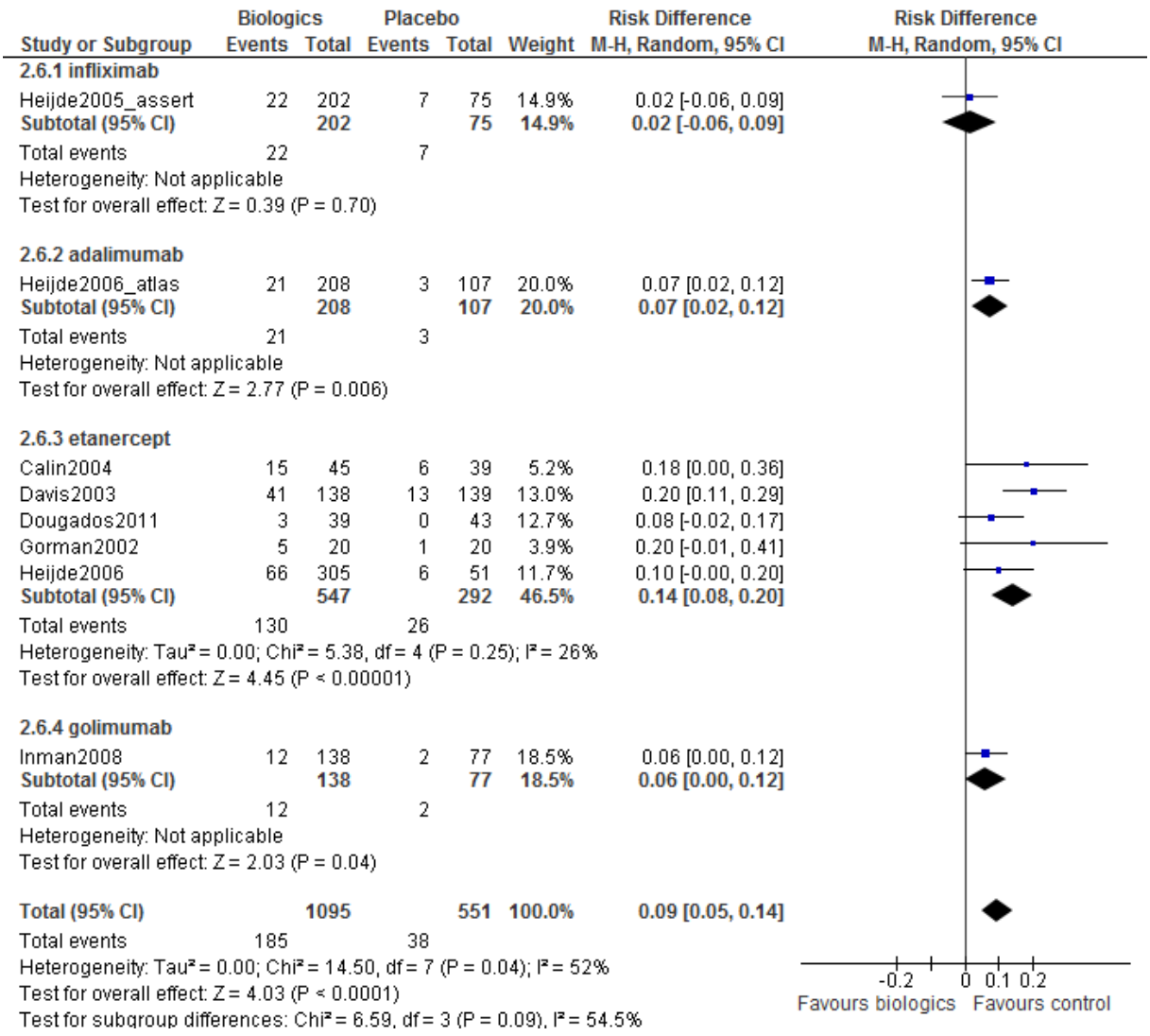
Forest plot of comparison: Safety of biologicals – Infections



Forest plot of comparison: Safety of biologicals – Serious infections



Forest plot of comparison: Safety of biologicals – Injection stie reaction



8.7 Literature search strategies for cost-utility articles

Ovid MEDLINE(R) 1946 to Present with Daily Update, 11th April, 2013
Search strategy (number of hits):

1 economics/ (26558)
2 exp "Costs and Cost Analysis"/ (170666)
3 VALUE OF LIFE/ (5308)
4 economics, dental/ (1855)
5 exp economics, hospital/ (18518)
6 economics, medical/ (8493)
7 economics, nursing/ (3870)
8 economics, pharmaceutical/ (2417)
9 (econom$or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom$).ti,ab. (139598)
10 (expenditure$ not energy).ti,ab. (15965)
11 (value adj1 money).ti,ab. (19)
12 budget$.ti,ab. (16084)
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (316033)
14 ((energy or oxygen) adj cost).ti,ab. (2486)

15 (metabolic adj cost).ti,ab. (687)
16 ((energy or oxygen) adj expenditure).ti,ab. (14820)
17 14 or 15 or 16 (17335)
18 13 not 17 (315238)
19 letter.pt. (767716)
20 editorial.pt. (312781)
21 historical article.pt. (291220)
22 19 or 20 or 21 (1357819)
23 18 not 22 (293153)
24 Animals/ (5083309)
25 Humans/ (12745180)
26 24 NOT (24 AND 25) {Including Related Terms} (14679)
27 23 not 26 (292897)
28 Ankylosing, Spondylitis/ (11149)
29 (etanercept or enbrel or tnfr-fc).ti,ab,rn. (4599)
30 (infliximab or remicade).ti,ab,rn. (7406)
31 (adalimumab or humira or D2E7).ti,ab,rn. (2721)
32 (golimumab or simponi).ti,ab,rn. (197)
33 29 or 30 or 31 or 32 (11054)
34 27 and 28 and 33 (31)
35 limit 34 to yr="2011 -Current" **(7)**

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <, 23rd April, 2012>
Search Strategy (number of hits):
1 (ankyl$ adj (spondylo$ or spondyli$)).ti,ab. (447)
2 (etanercept or enbrel or tnfr-fc).ti,ab,rn. (312)
3 (infliximab or remicade).ti,ab,rn. (603)
4 (adalimumab or humira or D2E7).ti,ab,rn. (288)
5 (golimumab or simponi).ti,ab,rn. (29)
6 2 or 3 or 4 or 5 (920)
7 1 and 6 (67)
8 (econom$or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom$).ti,ab. (10934)
9 (expenditure$ not energy).ti,ab. (1038)
10 (value adj1 money).ti,ab. (2)
11 budget$.ti,ab. (1712)
12 8 or 9 or 10 or 11 (13046)
13 7 and 12 **(3)**
Web of knowledge, http://apps.webofknowledge.com, 10th April, 2013
Number of hits and search strategy:
7 39
#5 NOT #6 Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2010-11-01 - 2013-04-09
# 6 322,154
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 Timespan=2010-11-01 - 2013-04-09
# 5 39
#4 AND #3 Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2010-11-01 - 2013-04-09
# 4 212,671
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 Timespan=2010-11-01 - 2013-04-09
# 3 374
#2 AND #1
Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2010-11-01 - 2013-04-09
# 2 4,315
TS=(etanercept or enbrel tnfr-fc or infliximab or remicade or adalimumab or humira or D2E7 or golimumab or simponi)
Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2010-11-01 - 2013-04-09
# 1 1,979
TS=(ankyl* same spondyl*)
Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2010-11-01 - 2013-04-09

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

See file at http://hecon.uni.corvinus.hu

Biologicals in Ankylosing Spondylitis – Appendix 8.8