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Biologics or tofacitinib for people with rheumatoid arthritis naive to methotrexate: a systematic review and network meta-analysis (Review)

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[Overview of Reviews]

Biologics or tofacitinib for people with rheumatoid arthritis naive to methotrexate: a systematic review and network meta-analysis

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ABSTRACT

Background

Biologic disease-modifying anti-rheumatic drugs (biologics) are highly effective in treating rheumatoid arthritis (RA), however there are few head-to-head biologic comparison studies. We performed a systematic review, a standard meta-analysis and a network meta-analysis (NMA) to update the 2009 Cochrane Overview. This review is focused on the adults with RA who are naive to methotrexate (MTX) that is, receiving their first disease-modifying agent.

Objectives

To compare the benefits and harms of biologics (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) and small molecule tofacitinib versus comparator (methotrexate (MTX)/other DMARDs) in people with RA who are naive to methotrexate.

Methods

In June 2015 we searched for randomized controlled trials (RCTs) in CENTRAL, MEDLINE and Embase; and trials registers. We used standard Cochrane methods. We calculated odds ratios (OR) and mean differences (MD) along with 95% confidence intervals (CI) for traditional meta-analyses and 95% credible intervals (CrI) using a Bayesian mixed treatment comparisons approach for network meta-analysis (NMA). We converted OR to risk ratios (RR) for ease of interpretation. We also present results in absolute measures as risk difference (RD) and number needed to treat for an additional beneficial or harmful outcome (NNTB/H).

Main results

Nineteen RCTs with 6485 participants met inclusion criteria (including five studies from the original 2009 review), and data were available for four TNF biologics (adalimumab (six studies; 1851 participants), etanercept (three studies; 678 participants), golimumab (one study;

637 participants) and infliximab (seven studies; 1363 participants)) and two non-TNF biologics (abatacept (one study; 509 participants) and rituximab (one study; 748 participants)).

Less than 50% of the studies were judged to be at low risk of bias for allocation sequence generation, allocation concealment and blinding, 21% were at low risk for selective reporting, 53% had low risk of bias for attrition and 89% had low risk of bias for major baseline imbalance. Three trials used biologic monotherapy, that is, without MTX. There were no trials with placebo-only comparators and no trials of tofacitinib. Trial duration ranged from 6 to 24 months. Half of the trials contained participants with early RA (less than two years' duration) and the other half included participants with established RA (2 to 10 years).

Biologic + MTX versus active comparator (MTX (17 trials (6344 participants)**/MTX + methylprednisolone** 2 trials (141 participants)**)**

In traditional meta-analyses, there was moderate-quality evidence downgraded for inconsistency that biologics with MTX were associated with statistically significant and clinically meaningful benefit versus comparator as demonstrated by ACR50 (American College of Rheumatology scale) and RA remission rates. For ACR50, biologics with MTX showed a risk ratio (RR) of 1.40 (95% CI 1.30 to 1.49), absolute difference of 16% (95% CI 13% to 20%) and NNTB = 7 (95% CI 6 to 8). For RA remission rates, biologics with MTX showed a RR of 1.62 (95% CI 1.33 to 1.98), absolute difference of 15% (95% CI 11% to 19%) and NNTB = 5 (95% CI 6 to 7). Biologics with MTX were also associated with a statistically significant, but not clinically meaningful, benefit in physical function (moderate-quality evidence downgraded for inconsistency), with an improvement of HAQ scores of -0.10 (95% CI -0.16 to -0.04 on a 0 to 3 scale), absolute difference -3.3% (95% CI -5.3% to -1.3%) and NNTB = 4 (95% CI 2 to 15).

We did not observe evidence of differences between biologics with MTX compared to MTX for radiographic progression (low-quality evidence, downgraded for imprecision and inconsistency) or serious adverse events (moderate-quality evidence, downgraded for imprecision). Based on low-quality evidence, results were inconclusive for withdrawals due to adverse events (RR of 1.32, but 95% confidence interval included possibility of important harm, 0.89 to 1.97). Results for cancer were also inconclusive (Peto OR 0.71, 95% CI 0.38 to 1.33) and downgraded to low-quality evidence for serious imprecision.

Biologic without MTX versus active comparator (MTX 3 trials (866 participants)

There was no evidence of statistically significant or clinically important differences for ACR50, HAQ, remission, (moderate-quality evidence for these benefits, downgraded for imprecision), withdrawals due to adverse events,and serious adverse events (low-quality evidence for these harms, downgraded for serious imprecision). All studies were for TNF biologic monotherapy and none for non-TNF biologic monotherapy. Radiographic progression was not measured.

Authors' conclusions

In MTX-naive RA participants, there was moderate-quality evidence that, compared with MTX alone, biologics with MTX was associated with absolute and relative clinically meaningful benefits in three of the efficacy outcomes (ACR50, HAQ scores, and RA remission rates). A benefit regarding less radiographic progression with biologics with MTX was not evident (low-quality evidence). We found moderate- to low-quality evidence that biologic therapy with MTX was not associated with any higher risk of serious adverse events compared with MTX, but results were inconclusive for withdrawals due to adverse events and cancer to 24 months.

TNF biologic monotherapy did not differ statistically significantly or clinically meaningfully from MTX for any of the outcomes (moderate-quality evidence), and no data were available for non-TNF biologic monotherapy.

We conclude that biologic with MTX use in MTX-naive populations is beneficial and that there is little/inconclusive evidence of harms. More data are needed for tofacitinib, radiographic progression and harms in this patient population to fully assess comparative efficacy and safety.

PLAIN LANGUAGE SUMMARY

Biologics for rheumatoid arthritis (RA) in people not previously treated with methotrexate (MTX)

Review question

We studied the benefits and harms of biologics or tofacitinib on people with rheumatoid arthritis (RA) who have not previously been treated with methotrexate (MTX), in trials done until June 2015. Data was available for four TNF biologics (adalimumab, etanercept, golimumab, infliximab) and two non-TNF biologics (abatacept, rituximab).

What is RA and what are biologics/tofacitinib?

In RA, the immune system, which normally fights infection, attacks the joint lining making it inflamed. Without treatment, the inflammation can lead to joint damage and disability. Biologics or tofacitinib are medications that can reduce joint inflammation/damage and improve symptoms.

The review shows that in people with RA:

- Biologics (abatacept, adalimumab, etanercept, golimumab, infliximab, rituximab) in combination with MTX probably improve signs and symptoms of RA (tender or swollen joints), the chances of RA remission (disappearance of symptoms) and probably slightly improve functional ability. We downgraded our confidence in the results because of concerns about the inconsistency of some results.

- Biologics in combination with MTX may make little or no difference in the risk of serious adverse events or withdrawals due to adverse events. We downgraded our confidence in the results because of concerns about the inconsistency of some results and the lack of data.

- We often do not have precise information about side effects and complications. Because of the lack of data, we are uncertain of the effect of biologics on the risk of cancer.

-TNF biologics (adalimumab, etanercept, golimumab) alone (not in combination with MTX) probably make little or no difference in signs and symptoms of RA or chances of RA remission (no data for non-TNF biologics alone).

Best estimate of what happens to people with RA when taking biologics:

ACR50 (American College of Rheumatology 50: number of tender or swollen joints, pain and disability) :

Biologic + MTX versus MTX: 56 people out of 100 who were on a biologic (in combination with MTX) experienced improvement in RA compared to 40 people out of 100 who were on MTX (16% improvement).

Biologic monotherapy (TNF biologics) versus MTX: 35 people out of 100 who were on a biologic experienced improvement in RA compared to 37 people out of 100 who were on MTX (2% reduction)

Remission (DAS <1.6 or DAS28 < 2.6)

Biologic + MTX versus MTX: 37 people out of 100 who took a biologic (in combination with MTX) had their RA symptoms disappear compared to 22 people out of 100 who were on MTX (15% improvement).

Biologic monotherapy (TNF biologics) versus MTX: 22 people out of 100 who took a biologic had their RA symptoms disappear compared to 20 people out of 100 who were on MTX (2% improvement).

Progression of disease damage as measured on X-rays (scale 0 to 448)

Biologic + MTX versus MTX: people who took a biologic (in combination with MTX) showed radiographic progression of 0.45 points compared to those on MTX who showed progression of 3 points (0.5% reduction).

There were no studies for biologic monotherapy.

Drug withdrawal due to adverse events

Biologic + MTX versus MTX: 7 people out of 100 who took a biologic (in combination with MTX) withdrew from the study due to adverse events compared to 5 out of 100 participants who took MTX (2% more).

Biologic monotherapy (TNF biologics) versus MTX: 6 people out of 100 who took a biologic withdrew from the study due to adverse events compared to 6 out of 100 participants who took MTX (0% difference).

Serious adverse events

Biologic + MTX versus MTX: 11 participants out of 100 who took a biologic (in combination with MTX) reported serious adverse events compared to 10 participants out of 100 on MTX (1% more serious adverse events).

Biologic monotherapy (TNF biologics) versus MTX: 3 participants out of 100 who took a biologic reported serious adverse events compared to 7 participants out of 100 on MTX (4% fewer serious adverse events).

Cancer

The same number of people (1 out of 100) reported cancer for biologic (both alone and in combination with MTX) and the comparator MTX. However, there were few events of cancer so caution in this interpretation is needed.

BACKGROUND

Description of the condition

Rheumatoid Arthritis (RA) is a chronic inflammatory arthritis characterized by inflammation of the synovial lining of the joints, tendons and periarticular structures, with main disease features of joint pain, swelling and joint destruction (Lee 2001). RA affects 0.5% to 1.0% of the population (Kvien 2004) and frequently leads to health-related quality of life (HRQoL) deficits (Kvien 2005; Lubeck 2004), functional limitation, and in people with refractory disease, untreated disease or longer disease duration, or both, to joint destruction, severe disability and disfigurement (Odegard 2005; Yelin 2007).

Pharmacological treatment options for RA include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, traditional disease-modifying anti-rheumatic drugs (DMARDs), biologic DMARDs and oral small molecules (e.g. tofacitinib). Traditional DMARDs (referred to as DMARDs from here on), most commonly methotrexate (MTX), but also including sulfasalazine, hydroxychloroquine, leflunomide, cyclosporine etc., either alone or in combination, are usually the first choice drug for people with early or established RA; when these fail, biologics (alone or with DMARDs) or DMARD combinations or tofacitinib are treatment options (Singh 2012; Singh 2016a; Smolen 2014). DMARDs are the cornerstone of RA management since their use is associated with improvement in pain and physical function and a reduction in radiographic progression (Finckh 2006; Pincus 2002) and disability (Cash 1994; Strand 2008).

Description of the interventions

Biologics are newer treatment options available for treatment of RA. Biologics are medications that are made in live cell systems. Biologics are frequently categorized based on their mechanism of action. Two broad categories are biologics that do or do not inhibit tumor necrosis factor (TNF), a key cytokine in RA (Scott 2006). Further classification is based on whether the biologic is a receptor or an antibody (for TNF inhibitors), or the specific cytokine/pathway/cell they inhibit (non-TNF biologic). The currently approved biologics for the treatment of RA are:

1. TNF biologics
   a. monoclonal antibodies against the TNF (TNF antibody biologic)
      i. infliximab (Remicade, approved 1998 in the USA) (FDA 1998)
      ii. adalimumab (Humira, approved 2002) (FDA 2002)
      iii. certolizumab pegol (Cimzia, approved 2008) (FDA 2008)
      iv. golimumab (Simponi, approved 2009) (FDA 2009)
   b. Soluble TNF receptor
      i. etanercept (Enbrel, approved 1998) (FDA 1998a), that binds free-circulating TNF so that it does not bind to the cellular receptor.
2. Non-TNF biologics
   a. anti-CD28 therapy:
      i. abatacept (Orencia, approved 2005) (FDA 2005)
   b. anti-B-cell therapy:
      i. rituximab (Rituxan/Mabthera, approved 1997 for lymphoma and 2006 for RA) (FDA 1997;Drugs 2006)
   c. anti-interleukin (IL)-6 therapy:
      i. tocilizumab (Actemra, approved 2010) (FDA 2010)
   d. anti-IL-1 therapy:
      i. anakinra (Kineret, approved 2001) (FDA 2001)

Tofacitinib (XELJANZ), an oral small molecule drug, (FDA 2012), was approved in 2012 in the USA. Biologics or tofacitinib provide clinically important improvements in pain, function and HRQoL in people not responding to traditional DMARDs such as methotrexate (MTX) (Boyce 2016; Strand 2008). Although biosimilars (generic medications for biologics) are available in the USA, Europe and other regions, these were not available at the literature review cut-off. Therefore, our network meta-analysis and systematic review includes biologics or tofacitinib.

How the intervention might work

Systemic and joint inflammation in RA is mediated by the activation of several potential targets including T-cells (Cope 2008), B-cells (Buggati 2014), macrophages (Szekanecz 2007), and other immune cells (Woolley 2003) in response to an environmental trigger/antigen, associated with expression of chemokines, metalloproteinases and inflammatory cytokines (TNF-alpha, IL-1, IL-6 etc.) (Brennan 2008; Choy 2001) and activation of host cells such as fibroblasts, osteoclasts and chondrocytes leading to bone and cartilage destruction, a hallmark of RA (Brennan 2008; Connell 2006). Treatment guidelines published recently (Saag 2008; Singh 2012; Singh 2016a; Smolen 2014) and consensus statements (Furst 2008; Furst 2010; Furst 2012) highlight the current evidence and the role of biologics or tofacitinib in the management of RA.

Why it is important to do this overview

Biologics are used in a variety of scenarios, most commonly when someone has a sub-optimal response (DMARD/MTX-inadequate responders (MTX-IR)) or intolerance to traditional DMARDs such as MTX (Singh 2016a). Tofacitinib is also used in this patient population. It is not well known what role, if any, these drugs can play in the treatment of people with RA who are MTX-naive, although this is not a current treatment option in many countries due to their greater costs. It is not clear whether or not they are more effective than traditional DMARDs and how the harms compare to traditional DMARDs in people with RA who are MTX-naive.

Existing Cochrane systematic reviews of biologics have included trials that evaluated the benefits and harms of single biologics compared with either placebo, MTX or other DMARDs. But to inform choice of biologic, data about the comparative benefits and harms of different biologics is needed. Ideally, evaluation of comparative effectiveness requires head-to-head comparison studies, but when these are scant (Gabay 2013; Schiff 2008a; Weinblatt 2013), indirect comparisons that use a common comparator may be informative (Song 2003). Use of all available data from both direct and indirect comparisons is the essence of network meta-analysis (NMA). Our review differs from the usual systematic reviews, in that it is not intended to examine only one intervention for RA but aims to systematically review and simultaneously compare the existing randomized trials of biologics or tofacitinib for RA and, while doing so, consider both direct and indirect evidence using a network meta-analysis (NMA) (Becker 2008; Puhan 2014).

Our previous overview and NMA of biologics for RA was performed in 2009 (Singh 2009) and is ready for an update. Due to feasibility

issues, an a priori decision was made to examine use of biologics or tofacitinib in four RA populations separately:

1. methotrexate-naive (people who have not previously been treated with methotrexate; MTX-naive) (**this publication**);
2. methotrexate/disease-modifying anti-rheumatic drug incomplete (inadequate) responder (MTX/DMARD-IR, that is, people whose treatment with MTX/DMARDs failed due to lack of efficacy (primary or secondary), adverse event, patient preference etc. or a combination of these reasons), assessing the effect of biologic + MTX/DMARD (Singh 2016b);
3. methotrexate/disease-modifying anti-rheumatic drug incomplete (inadequate) responder (MTX/DMARD-IR), assessing the effect of biologic monotherapy (Singh 2016c); and
4. biologic-experienced (people whose treatment with biologic failed due to lack of efficacy (primary or secondary), adverse event, cost, patient preference etc. or a combination of these reasons (Singh 2017).

OBJECTIVES

To compare the benefits and harms of biologics (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) and small molecule tofacitinib versus comparator (methotrexate (MTX)/other DMARDs) in people with RA who are naive to methotrexate.

METHODS

Criteria for considering reviews for inclusion

NOTE: this update uses individual studies, not reviews, for the basis of all analyses.

Randomized controlled trials (RCTs) of biologics or tofacitinib for RA in people who are MTX-naive.

Types of studies

Our 2009 review only included studies that examined the efficacy/safety of standard-dose biologics. for the 2015 update we expanded our inclusion criteria to include studies with any dose of biologic, provided they had clinically relevant outcomes. We included all nine approved biologics for RA (TNF biologics (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) and non-TNF biologics (abatacept, anakinra, rituximab, tocilizumab)) and also searched for trials of tofacitinib.

Types of participants

Adults 18 years or older, with RA meeting the 1987 American College of Rheumatology (ACR) classification criteria for RA (Arnett 1988) or the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA (Aletaha 2010), who are MTX-naive.

Types of interventions

TNF biologics: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab; or non-TNF biologics: abatacept, anakinra, rituximab, tocilizumab; or tofacitinib used alone or in combination with traditional DMARD/other biologic compared to placebo alone or to placebo plus traditional DMARDs or biologics or combinations of DMARDs.

Types of outcome measures

Primary/major outcomes

We pre-specified seven outcomes, ACR50, Health Assessment Questionnaire (HAQ), RA disease remission, radiographic progression, withdrawals due to adverse events, serious adverse events (SAEs) and cancer.

1. ACR50, defined as 50% improvement in both tender and swollen joint counts and 50% improvement in at least three of the following five variables: patient global assessment, physician global assessment, pain score, function measurement with instruments such as HAQ score, and acute phase reactant (erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) (Chung 2006; Felson 1995). We chose ACR50, as clinical and statistical evidence supports this as the preferred endpoint for contemporary RA clinical trials (Ghogomu 2014). We specified that we would assess outcomes at the longest duration of follow-up. Most RA trials assess benefits and harms outcomes between four and six months, with some trials assessing longer-term outcomes.
2. Function measured by HAQ score or modified HAQ calculated as score changes (Fries 1980; Pincus 1983) and the proportion achieving minimal clinically important difference on HAQ 0.22 or less (Wells 1993).
3. RA disease remission defined as DAS less than 1.6 or DAS28 less than 2.6 (Fransen 2005; Prevoo 1996).
4. Radiographic progression, as measured by Larsen/Sharp/modified Sharp scores (Larsen 1977; Sharp 1971; Van der Heijde 1989).
5. Withdrawals due to adverse events (Ioannidis 2004)
6. Serious adverse events (SAEs) (Ioannidis 2004)
7. Cancer

We recognize that RCTs included in this overview are limited in their ability to assess long term safety, since rare or delayed effects will not be detected. We therefore also searched websites of various regulatory agencies, including the US Food and Drug Administration (FDA), Health Canada and European Medicines Agency (EMA) to summarize warnings related to each of the biologics.

Search methods for identification of reviews

NOTE: this update uses individual studies, not reviews, for the basis of all analyses.

We conducted a search starting at the end date of last search and up to June 2015 (one search and analysis update to February 2014 and a second one to June 2015) for the 2015 update. A Cochrane Information Specialist (TR) conducted an updated search for the 2015 update to identify individual studies in multiple databases, namely: the Cochrane Central Register of Controlled Trials (CENTRAL; in The Cochrane Library, 2015, Issue 1), MEDLINE (via OVID 1946 to 11 February 2015), and Embase (via OVID 1947 to 11 February 2015). We considered the 31 studies in the 2009 version (Singh 2009), which contained all people with RA, including those that were MTX-naive. We searched trials registers, including clinicaltrials.gov and the WHO trials register for ongoing studies, who.int/ictrp/en/.

Data collection and analysis

Selection of reviews

Two abstractors (SN/TC) reviewed the results of the search (titles and abstracts), and obtained the full texts of articles identified as relevant for this update.

Data extraction and management

Two pairs of abstractors (SN/TC; TC/JS), within each pair, independently extracted data from the reviews using a predefined data extraction form created as a Microsoft Excel® spreadsheet for the 2015 update and independently abstracted additional data for all doses (SN/JS) and additional outcomes, since the original review only included standard doses of biologics and not all outcomes were the same. TC double-checked all data for accuracy after the initial abstraction.

We resolved disagreements by discussion with JS or GW, as appropriate. We obtained additional information from the original RCTs where necessary, from the online supplementary materials or by contacting study authors. AM and JS designed the spreadsheets.

Assessment of methodological quality of included reviews

NOTE: this update uses individual studies, not reviews, for the basis of all analyses.

Two abstractors (JS/TC; SN/TC) independently evaluated the risk of bias of included studies and overall quality of the evidence as summarized below.

Risk of bias of included trials

Two abstractors (JS/ETG) independently assessed risk of bias for each included trial using the Cochrane 'Risk of bias' tool. We assessed the risk of bias on each of the following criteria: random sequence generation, allocation concealment, presence of blinding (participants, personnel, and outcome assessors) in the studies, incomplete outcome data, and selective outcome reporting (Higgins 2011). The risk of bias was assessed as recommended: low risk, high risk, or unclear risk (either lack of information or uncertainty over the potential for bias). We resolved disagreements by discussion between the review authors.

Quality of evidence

Two review authors (JS and AM) independently assessed the overall quality of the evidence for each outcome using the GRADE approach (Guyatt 2008). The GRADE approach improves reliability in comparison to intuitive judgments about the certainty of a body of evidence (Mustafa 2013). The GRADE system specifies four levels of quality of evidence.

1. High quality for randomized trials; or double-upgraded observational studies.
2. Moderate quality for downgraded randomized trials; or upgraded observational studies.
3. Low quality for double-downgraded randomized trials; or observational studies.
4. Very low quality for triple-downgraded randomized trials; or downgraded observational studies; or case series/case reports.

Randomized trial evidence could be downgraded by one or two levels depending on the presence of five factors.

1. Serious (-1) or very serious (-2) limitation to study quality
2. Important inconsistency (-1)
3. Some (-1) or major (-2) uncertainty about directness
4. Imprecise or sparse data (-1)
5. High probability of reporting bias (-1)

Data synthesis

Statistical analyses

We performed the standard and NMA analyses including important factors such as the route of biologic (intravenous versus subcutaneous), dose (low dose (LD) versus standard dose (SD) versus high dose (HD)) and concomitant MTX/DMARD, for the 2015 update. We also performed pre-specified analyses for subgroups by trial and RA disease duration, since they might contribute to differences in benefits and harms of biologics. In order to handle rare events in direct comparison meta-analyses, we used Peto's odds ratios as the effect measure. For other outcomes, we used odds ratio (OR) or mean difference (MD) as effect measures. We considered P values less than 0.05 and 95% confidence intervals (CI) or credible intervals (CrI) that did not include 1 to be statistically significant.

The standard meta-analysis (direct comparisons) determined the effectiveness of treatments directly compared to each other and was performed using Review Manager 5 (RevMan5) (RevMan 2014). We used the I^2 statistic for quantifying heterogeneity of the results in individual studies (Higgins 2003), since heterogeneity is a common issue encountered while performing meta-analyses (Higgins 2002; Thompson 1999). This statistic combines the Chi^2 statistic and the number of studies contributing to each summary estimate in the figure. In all the forest plots presenting effect measure data per treatment, we applied the random-effects model as the default option (DerSimonian 2007) for illustrative purposes. We estimated the number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH), with 95% CIs on the basis of the derived OR comparing treatment to control and considering the overall event rate in the placebo group as a proxy for the community baseline event rate. This method enables direct translation into clinical practice (Osiri 2003), using Visual Rx with the overall (pooled) number of responders within the available studies as proxy for the expected rate of responders in a given RA population (Cates 2009).

We conducted a network meta analysis (NMA) based on a Bayesian mixed treatment comparison (MTC) approach, using the WinBUGS statistical software for the Bayesian analysis (MRC Biostatistics Unit, Cambridge, UK) (Spiegelhalter 2003). We performed a Markov Chain Monte Carlo (MCMC) simulation with at least 5000 or more iterations (as needed) to derive the corresponding 95% CrIs. We used informative priors for the variance parameters (Turner 2012). Where considered more suitable, we used vague priors for basic parameters. Assessment of model fit for the NMA was based on deviance information criterion (DIC) and comparison of residual deviance (Spiegelhalter 2003). We assessed trace plots and the Brooks-Gelman-Rubin statistic to ensure that convergence was reached (Spiegelhalter 2003). We applied the continuity correction for zero event cells to make non-zero cells where needed. In order to

assess inconsistency (conflict between direct and indirect evidence (Wells 2009), we compared deviance and deviance information criteria (DIC) statistics in fitted consistency and inconsistency models (Dias 2011) and examined the inconsistency plot. We chose between the random-effects model and the fixed-effect model based on the assessment of the DIC and comparison of residual deviance to number of unconstrained data points.

We used OR as effect measure for dichotomous outcomes, that is, the number of participants achieving ACR50, remission, serious adverse events, and withdrawals due to adverse events; and MD for continuous outcomes such as HAQ and radiographic progression. For cancer data, we anticipated that events would be rare (Bradburn 2007; Sweeting 2004). In order to handle these expected sparse data, we applied an empirical Bayes (treatment arm-based) approach (Salanti 2008). AK and AH performed data analyses, under the supervision of GW.

Sub-group analyses/planned comparisons

In addition to the biologic + MTX versus comparator and biologic alone (monotherapy) versus comparator analysis, we conducted the following a priori subgroup analyses using the standard meta-analysis or NMA.

1. By type of biologic: TNF biologics versus non-TNF biologics
2. By type of biologic, receptor versus antibody: medications targeting TNF receptor (etanercept) versus monoclonal antibodies against TNF (adalimumab, certolizumab pegol, golimumab, infliximab) versus non-TNF biologic
3. By biologic dose: high-dose (HD) versus standard-dose (SD) versus low-dose (LD) biologic. We expanded the definitions of standard dose of each biologic from 2009 to include the newer biologics and tofacitinib, as follows:
   a. abatacept intravenous: every four weeks intravenously at 500 mg dose in people weighing less than 60 kg, 750 mg in people weighing 60 kg to 100 kg and 1000 mg in people weighing more than 100 kg, after the initial dosing regimen of baseline, two- and four-week infusions;
   b. abatacept subcutaneous: 125 mg subcutaneous weekly;
   c. adalimumab: 40 mg subcutaneous every two weeks;
   d. anakinra: 100 mg subcutaneous every day;
   e. certolizumab pegol: 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week (for maintenance dosing, 400 mg every four weeks can be considered);
   f. etanercept: 25 mg subcutaneous twice weekly or 50 mg subcutaneous once weekly;
   g. golimumab: 50 mg administered by subcutaneous injection once a month;
   h. infliximab: 3 mg/kg intravenous every eight weeks after initial dosing at 0, 2 and 6 weeks;
   i. rituximab: two 1000 mg intravenous doses two weeks apart;
   j. tocilizumab intravenous: starting dose is 4 mg per kg every four weeks followed by an increase to 8 mg per kg every four weeks based on clinical response;
   k. tocilizumab subcutaneous: 162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response for people weighing less than 100 kg, and 162 mg administered subcutaneously every week for people weighing 100 kg or more;
   l. tofacitinib: 5 mg orally twice a day, or 10 mg once daily.

The following subgroup analyses, specified a priori, were also performed using NMA.

1. Trial duration: short duration (six months or less), intermediate duration (between six and 12 months) or long duration (more than 12 months)
2. RA disease duration: early RA (mean/median duration of less than two years) (Boers 2001), established RA (mean/median duration 2 to 10 years) or late RA (mean/median duration more than 10 years) (Barlow 1999).

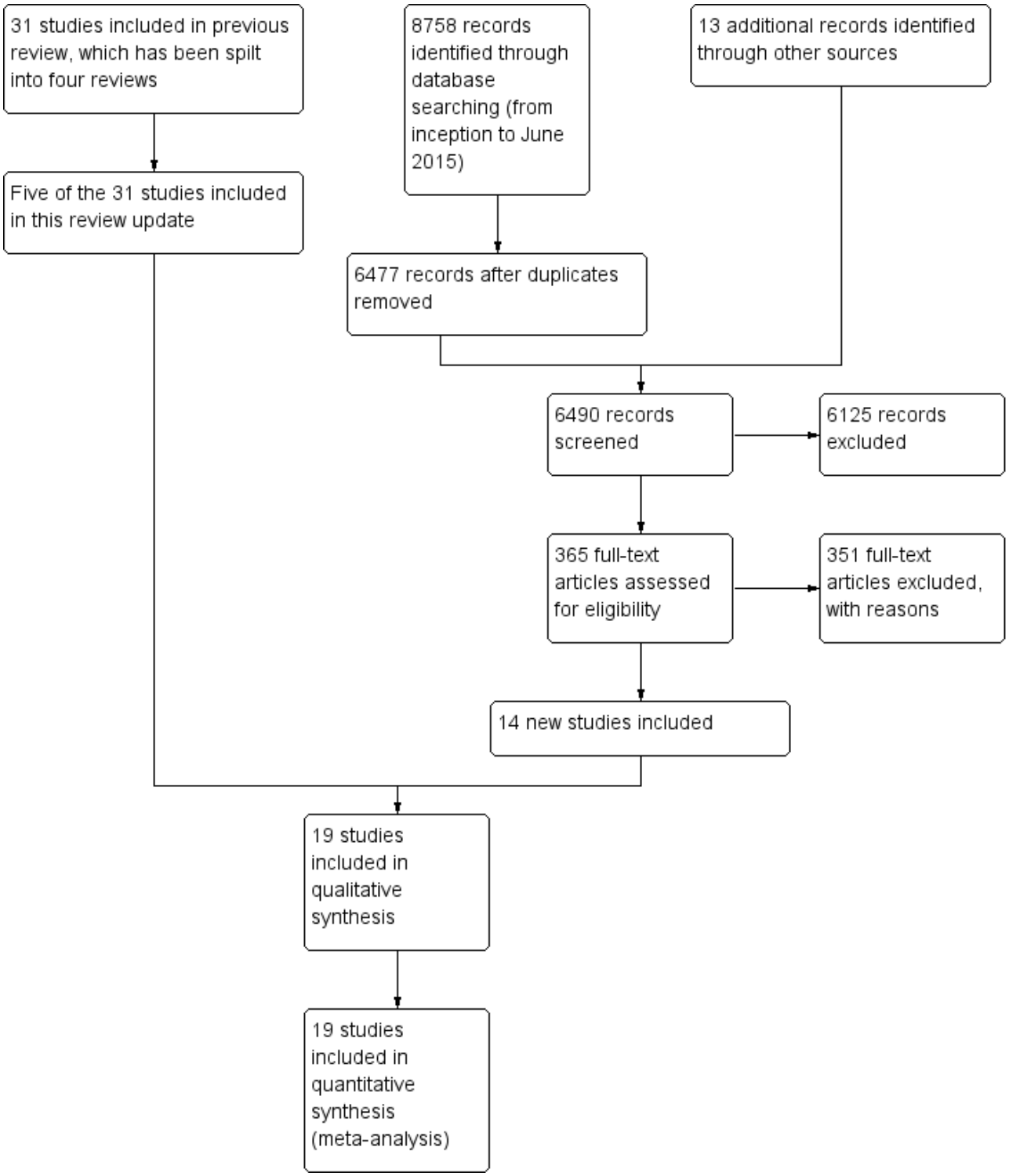
RESULTS

Description of included reviews

NOTE: this update uses individual studies, not reviews, for the basis of all analyses.

Figure 1 shows the overall study selection process. We identified a total of 19 trials from 8771 titles (including five of the 31 RCTs from the Cochrane Reviews in our original 2009 overview), including 6485 MTX-naive participants. Data for analyses were available from all trials. In 17 trials the comparator was MTX, while MTX + methylprednisolone was the comparator in two studies (Durez 2007; Nam 2014a). Therefore, we refer to the comparator as "MTX" for simplicity throughout the Results, Abstract, Plain language summary, Discussion and tables.

Figure 1. Study flow diagram



Characteristics of included studies are provided in Table 1. Study sample size ranged from 20 to 1049 participants. Nine studies were performed in participants with established RA (2 to 10 years), nine studies were performed in participants with early RA (less than two years) and one study included participants with unclear disease duration. These studies included four TNF biologics (adalimumab, etanercept, golimumab and infliximab) and two non-TNF biologics (abatacept and rituximab).

Eighteen trials included a biologic + MTX as the intervention of interest. Only one trial studied a biologic monotherapy (etanercept) (Marcora 2006). Most (n = 14) studies had a duration of 6 to 13 months, while five studies had a duration of 24 months or greater.

We found no tofacitinib studies eligible for inclusion, since in the only study that enrolled participants who were MTX-naive (Lee 2014), more than one-third of the participants were not naive to other traditional DMARDs and data were not reported separately.

Three hundred and fifty-one studies were excluded, and the main reasons for exclusion were wrong drug exposure, duplicate studies or abstracts. One hundred and twenty-six of the 351 excluded studies were included in the other split updates. See additional details in Appendix 1. Ongoing trials listed in trial registers are provided in Appendix 2.

Methodological quality of included reviews

For the 2015 update, two reviewers abstracted these study characteristics from the published reports of the individual trials.

Risk of bias of included trials in the 2015 update

Detailed 'Risk of bias' assessments for each trial including the reasons for each judgment are available at the Cochrane Musculoskeletal website Risk of bias A and Risk of bias B.

Allocation (selection bias)

All trials were described as randomized, however, only eight of 19 (42%) reported adequate sequence generation and we assessed them as low risk, while 11 (58%) did not describe the method used and we assessed them as unclear risk. We assessed allocation concealment as low risk in seven (37%) trials, unclear in 11 (58%) trials, and high risk in one (5%) trial.

Blinding (performance and detection bias)

We judged a total of eight (42%) trials at low risk of performance bias, and seven (37%) at unclear risk of bias. In four (21%) trials, participants were not blinded and these trials were at high risk of performance bias.

We assessed low risk of detection bias in nine (47%) trials, high risk of detection bias in three (16%) and unclear risk in seven (37%) trials.

Incomplete outcome data (attrition bias)

We judged more trials (10 out of 19; 53%) at low risk of attrition bias and nine (47%) trials were at high risk of attrition bias because more than 20% of participants withdrew/dropped out.

Selective reporting (reporting bias)

We judged four (21%) trials at low risk of bias and fifteen (79%) trials as unclear risk, since the study protocols were not available and we did not have enough information in the study report to assess selective reporting.

Other potential sources of bias

We assessed major baseline imbalance and 17 (89%) trials had low risk of bias, and two (11%) had high risk of bias.

Effect of interventions

In comparison to the original 2009 version, the 2015 update has several new key aspects:

1. instead of six biologics, we included all nine biologics and tofacitinib in our search although only studies from six biologics met the criteria for this review;
2. we included cancer and serious adverse events as outcomes;
3. we included all doses of biologics and analyzed by dose;
4. we analyzed outcomes by whether MTX/other DMARDs were used concomitantly or not; and
5. we used a Bayesian approach rather than a frequentist approach for analyses and reported odds ratios and 95% CrI.

For the 2015 version, we extracted all relevant data from the included RCTs. We pre-specified 7 outcomes, ACR50, HAQ, RA disease remission, radiographic progression, withdrawals due to adverse events, serious adverse events (SAEs) and cancer. Analyses and comparisons for all pre-specified outcomes were performed where data were available.

We followed the principles below while describing results to keep this review as comprehensive as possible.

1. We first present the odds ratios for the biologic + MTX and biologic alone (monotherapy) versus comparator, followed by pre-specified comparisons (e.g. TNF versus non-TNF biologic), followed by subgroup analyses, where data were available.
2. In the odds ratio analyses, only the last set of odds ratios compare the biologic by dose; other analyses prior to the dose analysis include all doses and provide comparison by a different characteristic of interest, for example, the type of biologic.
3. In the main analyses, when not specified, the biologic is in standard dose. We specify high dose and low dose in every instance when considered.
4. For biologics that are approved for only one route of administration (i.e. intravenous or subcutaneous only), we do not specify the route. The mention of the drug without the route implies that the only approved route for the drug was: subcutaneous (SC) for adalimumab, certolizumab pegol, etanercept and golimumab; intravenous (IV) for infliximab, and rituximab. Since only two biologics are approved for both subcutaneous and intravenous use (tocilizumab and abatacept), we specify these routes when describing results for abatacept. For other biologics, when not specified, the approved route of use is implicit. We recognize that some trials prior to approval of biologics used a different route in many cases (e.g. intravenous for golimumab).
5. We refer to the lack of statistical significance at $P < 0.05$ as 'not associated' or 'not significantly associated'. We also have additional comments about clinical significance, where applicable.

'Summary of findings' table

The 'Summary of findings' table presents both the direct estimates of biologics versus MTX with the quality of evidence followed by estimates from the NMA with the quality of evidence (Table 2). Absolute and risk ratio differences are provided for each estimate. We converted from OR in the NMA to RR in the 'Summary of findings' table and Abstract for ease of interpretation for clinicians.

Direct estimates were fairly consistent with the NMA estimates for all seven outcomes. There was moderate-quality evidence (downgraded for inconsistency) that biologics were associated with superior clinically meaningful and statistically significant

improvements versus comparator in ACR50 and RA disease remission and physical function as measured by the HAQ did show a statistically significant difference but was not clinically meaningful. There was low-quality evidence (downgraded for inconsistency and imprecision) that radiographic progression was not clinically meaningfully or statistically significantly reduced in those on biologics versus MTX. Based on moderate-quality evidence, results for serious adverse events showed no statistically significant or clinically meaningful differences. Based on low-quality evidence, results for withdrawals due to adverse and cancer were inconclusive, since the estimates included null effect as well as possibility of important harm.

Findings separately by TNF biologic and non-TNF biologic

In standard meta-analysis, based on high-quality evidence, biologic + MTX was also associated with statistically significant and clinically meaningful higher odds of ACR50 compared to the comparator in both TNF biologic and non-TNF biologic subgroups with risk ratio (RR) of 1.44 (95% CI 1.34 to 1.54) and 1.27 (95% CI 1.14 to 1.42) and absolute difference 17% (95% CI 13% to 21%) and 13% (95% CI 7% to 19%), and NNTB = 6 (95% CI 5 to 8) and = 8 (95% CI 6 to 14), respectively. Results were similar for the NMA.

In standard meta-analysis, based on low-quality evidence, compared to MTX, TNF biologic + MTX was associated with lower HAQ scores with better HAQ score improvement with mean difference of -0.09 (95% CI -0.26 to 0.07), which was neither statistically significant nor clinically meaningful. Based on moderate-quality evidence, non-TNF biologic + MTX was associated with better HAQ scores with statistically significant and clinically meaningful HAQ score improvement with a mean difference of -0.22 (95% CI -0.26 to -0.18) and an absolute difference of -7.3% (95% CI -8.7% to -6%) compared to MTX. Results did not show evidence of a clinically meaningful or statistically significant difference in TNF biologic monotherapy versus MTX.

In standard meta-analysis, based on moderate-quality evidence, TNF biologic + MTX showed a statistically significant and clinically meaningful higher rate of remission with RR of 1.55 (95% CI 1.22 to 1.96) and absolute difference 14% (95% CI 9% to 19%) and NNTB = 7 (95% CI 5 to 10), as did non-TNF biologic + MTX with RR 2.10 (95% CI 1.45 to 3.04), absolute difference 19% (95% CI 15% to 24%) and NNTB = 6 (95% CI 4 to 9). Results were similar in the NMA.

In standard meta-analysis, based on low-quality evidence, TNF biologic + MTX showed a non-statistically significant improvement in radiographic progression versus MTX with risk ratio of -3.18 (95% CI -6.80 to 0.43), absolute difference -0.71% (95% CI -1.52% to 959%). In NMA, this comparison was statistically significant with a difference of -3.73 (95% CrI -5.78 to -1.62), absolute difference , -0.83% (95% CI -1.29% to -0.36%) and NNTB = 3 (95%CI, 3 to 7), but the clinical significance of this difference was unclear. Non-TNF biologic + showed a much lower non-statistically significant improvement with an RR of -0.40 (95% CI -2.04 to 1.18), absolute difference -0.22% (95% CI -0.46% to 0.26%), which was also not significantly different in the NMA.

In standard meta-analysis, based on moderate-quality evidence, there was a clinically meaningful and statistically significant difference in increase in withdrawals due to adverse events in TNF biologic + MTX versus MTX with a RR of 1.60 (95% CI 1.10 to 2.32), absolute difference 3% (95% CI 1% to 4%) and NNTH = 35 (95% CI 17 to 183). Based on low-quality evidence, there was no evidence of a clinically meaningful and statistically significant difference in this outcome among the non-TNF biologic + MTX versus MTX, RR of 0.56 (95% CI 0.31 to 1.01), absolute difference -2% (95% CI -5% to 1%). Results were similar in the NMA.

In standard meta-analysis, based on moderate-quality evidence, there was no evidence of a statistically significant or clinically meaningful difference in serious averse events for TNF biologic + MTX versus MTX with a RR of 1.14 (95% CI 0.92 to 1.42), absolute difference 1% (95% CI -1% to 3%). Based on low-quality evidence, there was no evidence of a clinically meaningful and statistically significant difference in the non-TNF biologic + MTX versus MTX with a RR of 0.87 (95% CI 0.64 to 1.18), absolute difference -1% (95% CI -5% to 2%).

In standard meta-analysis, based on low-quality evidence, results were inconclusive for the risk of cancer for statistically significant or clinically meaningful difference for biologic + MTX versus MTX with a Peto's OR of 0.71 (95% CI 0.38 to 1.33) and an absolute difference of 0% (95% CI 0% to 0%). Results were also inconclusive for TNF biologic monotherapy versus MTX (there were no data for non-TNF monotherapy). Results were similar in the NMA.

Number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH)

For ACR50, HAQ and remission, NNTB for biologics + MTX were 7, 4 and 5, respectively. NNTB ranged from 6 to 8 for ACR50 among TNF and non-TNF biologic subgroups (both in combination with MTX). For HAQ, NNTB was 2 in the non-TNF biologic (+ MTX) subgroup. NNTBs ranged from 6 to 7 among TNF and non-TNF biologic subgroups for remission (both in combination with MTX). NNTBs for radiographic progression were not calculable for the direct comparisons but was 3 for the TNF biologic + MTX subgroup versus comparator in the NMA.

For the harms outcomes, only withdrawals due to adverse events provided an NNTH of 35 for the direct comparison for TNF biologic + MTX subgroup and 31 for the same subgroup in the NMA.

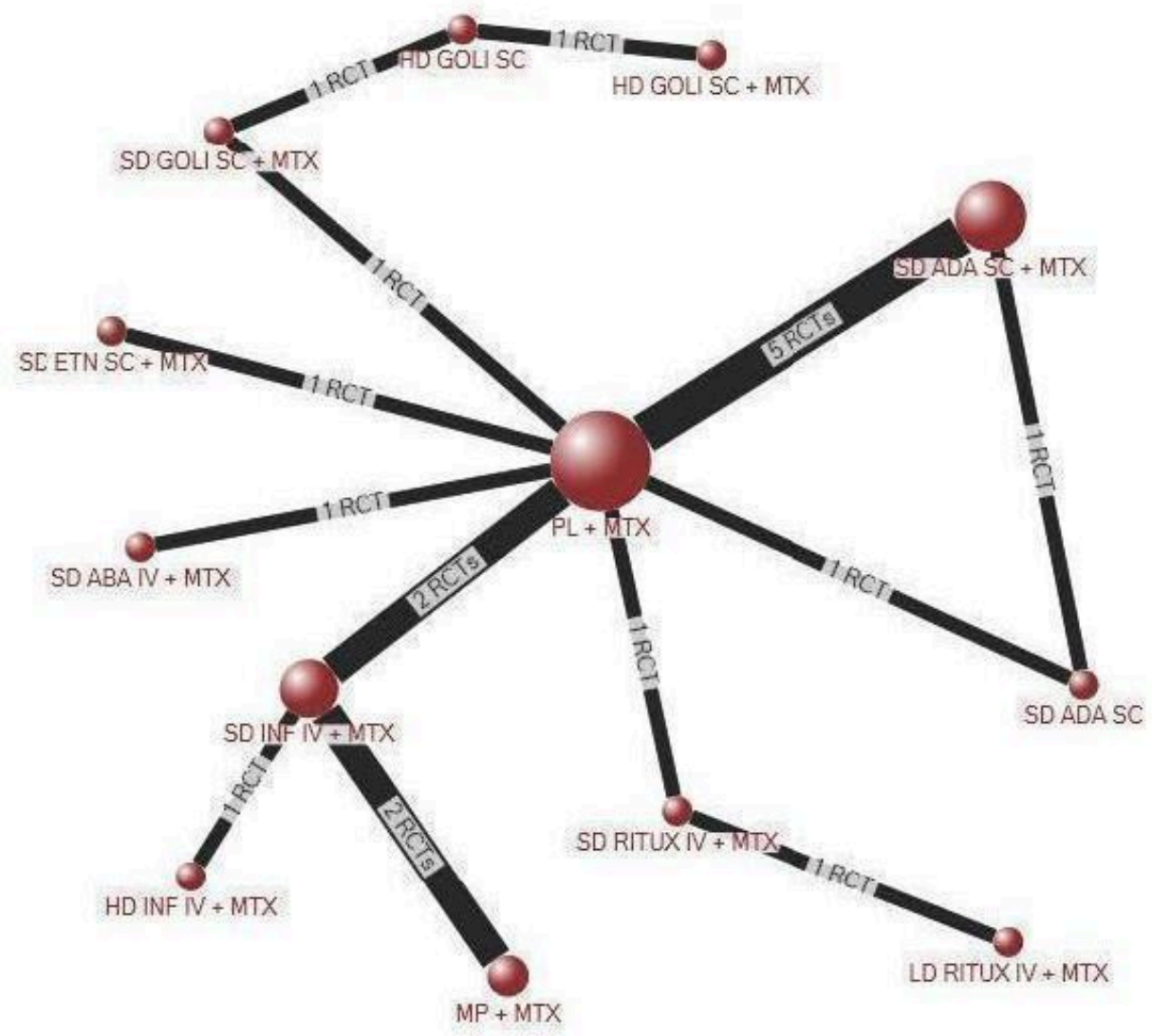
Since there were no statistically significant differences between TNF biologic monotherapy versus MTX (active comparator), NNTB and NNTH could not be calculated. All studies of biologic monotherapy were for TNF biologic monotherapy only, with none for non-TNF biologic monotherapy.

Main analysis: comparison of the biologics with regard to benefit and harm

Primary/major benefit outcome: ACR50

Fourteen studies with 6153 participants reported ACR50. Of these, all studies included at least one arm with participants on a biologic with concomitant MTX. An example of a network diagram for MTX-naive is shown in Figure 2 for ACR50.

Figure 2. Network diagram: ACR50 in people with rheumatoid arthritis who were MTX/other DMARD-naive

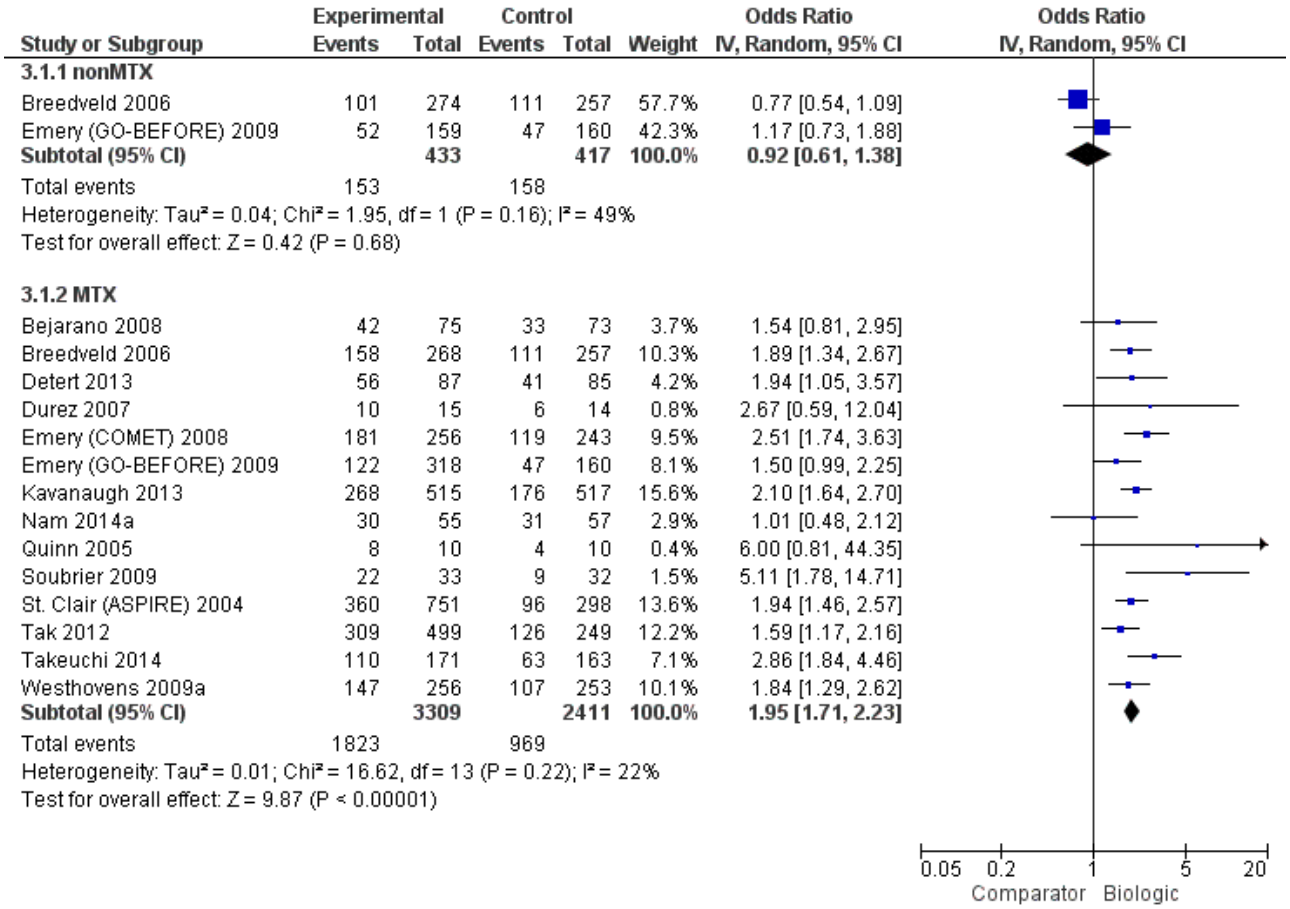


Odds ratios using standard meta-analyses

Biologic + MTX versus active comparator (mostly MTX) (14 studies)

Biologics + MTX were associated with a clinically meaningfully and statistically significantly higher odds of achieving an ACR50 response, OR 1.95 (95% CI 1.71 to 2.23), absolute difference of 16% (95% CI 13% to 20%) and NNTB = 7 (95% CI 6 to 8) with an I^2 of 22% indicating heterogeneity that might not be important; (Figure 3) (moderate-quality evidence).

Figure 3. ACR50: biologic (with and without concomitant MTX) versus comparator



Biologic without MTX versus active comparator (2 studies)

There was no evidence to indicate an effect of biologics without MTX compared to MTX, for achieving an ACR50 response, with an OR 0.92 (95% CI 0.61 to 1.38), absolute difference of -2% (95% CI -11% to 7%) with an I^2 of 49% indicating moderate heterogeneity; (Figure 3) (moderate-quality evidence).

Odds ratios by biologic type and dose using NMA

The overall rate of ACR50 by the type of biologic and the dose were as follows (14 studies, 6153 participants).

1. Type of biologic, TNF versus non-TNF biologic:
   a. biologic + MTX: compared to TNF biologic, non-TNF biologic was not associated with any statistically significant or clinically meaningful difference in the odds of ACR50, OR: 0.84 (95% CrI 0.57 to 1.23);
   b. biologic alone without MTX: no studies were available for analysis.
2. Type of biologic, etanercept versus TNF antibody biologic versus non-TNF biologic:
   a. biologic + MTX: compared to monoclonal TNF antibody biologic, neither non-TNF biologic nor etanercept were associated with any statistically significant or clinically meaningful differences in ACR50 rates, OR: 0.86 (95% CrI 0.56 to 1.28) and OR: 1.27 (95% CrI 0.72 to 2.25), respectively;
   b. biologic alone without MTX: no studies were available for analysis.
3. Biologic dose, SD versus LD versus HD biologic:
   a. biologic + MTX: compared to SD biologic, HD and LD biologic were not associated with any statistically significant or clinically meaningful differences in the odds of ACR50 at OR: 1.00 (95% CrI 0.74 to 1.33) and OR: 0.80 (95% CrI 0.53 to 1.20), respectively; LD was not statistically significantly less likely than HD to be associated with ACR50, OR: 0.80 (95% CrI 0.50 to 1.33);
   b. biologic alone without MTX: compared to SD biologic, HD biologic was associated with no statistically significant or clinically meaningful differences in odds of ACR50 at OR: 1.80 (95% CrI 0.98 to 3.30).

Main analyses using NMA

Fourteen RCTs (ten 2-arm, three 3-arm, and one 4-arm trial) enrolling 6153 participants provided data for all dose analyses (Appendix 3). Five SD biologics + MTX (adalimumab, rituximab, infliximab, etanercept, abatacept intravenous) were superior to placebo + MTX for ACR50 rates, with OR ranging from 1.84 to 2.52; HD infliximab + MTX was also superior to placebo + MTX. Five biologics in SDs + MTX (adalimumab, rituximab, infliximab, etanercept, abatacept) were superior to SD adalimumab monotherapy for ACR50 with OR ranging 2.08 to 3.08; HD infliximab

+ MTX was associated with 2.69-times odds compared to SD adalimumab monotherapy.

Subgroup analyses by RA disease duration (early versus established versus late RA)

Early RA (RA disease duration less than two years)

There were not enough data to perform NMA.

Established RA (disease duration 2 to 10 years)

Compared to placebo + MTX, SD adalimumab subcutaneous + MTX and SD etanercept + MTX, were associated with statistically significantly higher OR of ACR50 of 2.07 and 2.52, respectively. Compared to SD adalimumab subcutaneous, SD adalimumab subcutaneous + MTX and SD etanercept + MTX were associated with statistically significantly higher OR of ACR50: 2.58 and 3.13, respectively (3689 participants, 7 studies) (Appendix 4).

Late RA (disease duration more than 10 years)

There were not enough data to perform NMA.

Subgroup analyses by trial duration

Trial duration, six months or less

Compared to placebo + MTX, SD adalimumab subcutaneous + MTX was associated with 2.41-times higher odds of ACR50 (2240 participants, 5 studies) (Appendix 5).

Trial duration, between six and 12 months

Compared to placebo + MTX, SD infliximab + MTX was associated with 1.94-times higher odds of ACR50 (2106 participants, 5 studies) (Appendix 6).

Trial duration, between six and 12 months

Compared to placebo + MTX, SD adalimumab + MTX was associated with 1.78-times higher odds of ACR50. Compared to SD adalimumab subcutaneous, SD adalimumab subcutaneous + MTX was associated with 2.40-times higher OR of ACR50 (1695 participants, 3 studies) (Appendix 7).

Primary/major benefit outcome- HAQ

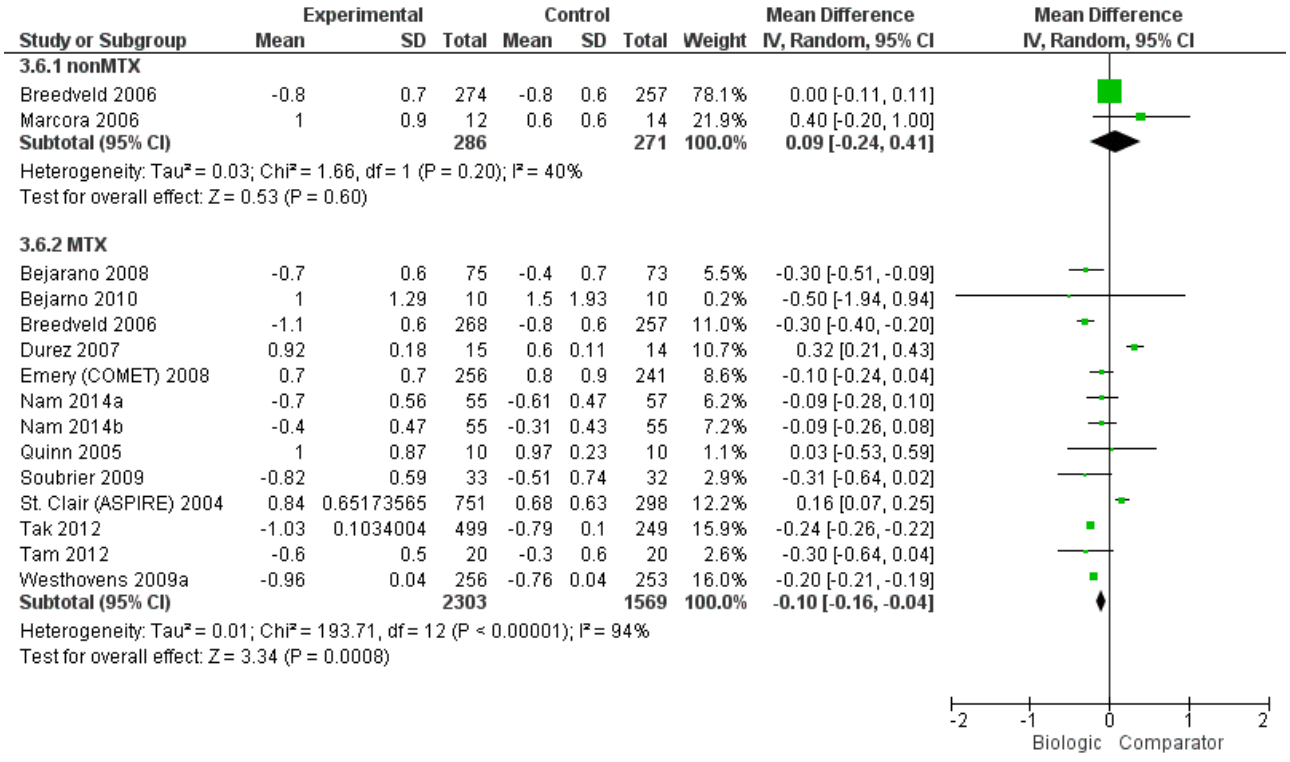
14 studies with 4,172 participants reported data on HAQ scores on a 0 to 3 scale. Of these, 13 studies included at least one arm with participants on a biologic with concomitant MTX and 1 study had only biologic without MTX).

Mean difference using standard meta-analyses

Biologic + MTX versus active comparator

Compared to MTX, biologic + MTX use was associated with a statistically significant mean difference (MD) in HAQ scores -0.10 (95% CI-0.16 to -0.04, absolute difference -3.3% (95% CI -5.3% to -1.3%), NNTB = 4 (95% CI 2 to 15) with I^2 = 94%) indicating considerable heterogeneity and the difference may not be clinically meaningful; (Figure 4) (moderate-quality evidence). When we excluded three studies contributing to high heterogeneity (Durez 2007; St Clair 2004; Tak 2012), biologic + MTX use was associated with a statistically significant and potentially clinically meaningful mean difference in HAQ scores -0.20 versus comparator (mostly MTX) (95% CI-0.25, -0.15), I^2 = 17%, indicating heterogeneity that might not be important.

Figure 4. HAQ: biologic (with and without concomitant MTX) versus comparator



Biologic without MTX versus active comparator

Compared to MTX, biologics without MTX was not associated with evidence of any statistically significant mean difference in HAQ scores 0.09 (95% CI -0.24 to 0.41, absolute difference 3% (95% CI -8% to 13.7%), I^2 = 40%) indicating moderate heterogeneity; this difference may not be clinically meaningful; (Figure 4) (moderate-quality evidence).

Odds ratios by biologic type and dose using NMA

The overall HAQ scores by the type of biologic and the dose was as follows (4,172 participants, 14 studies).

1. Type of biologic, TNF versus non-TNF biologic:
   a. biologic + MTX: compared to TNF biologic, non-TNF biologic did not show a significant or clinically meaningful difference in HAQ scores, MD: -0.14 (95% CrI -0.50 to 0.23);
   b. biologic alone without MTX: there were no studies to perform this analysis.
2. Type of biologic, etanercept versus TNF antibody biologic versus non-TNF biologic:
   a. biologic + MTX: compared to monoclonal TNF antibody biologic, neither non-TNF biologic nor etanercept were associated with any statistically significant or clinically meaningful differences in HAQ scores, MD: -0.13 (95% CrI -0.54 to 0.29) and MD: -0.01 (95% CrI -0.42 to 0.43), respectively. Compared to non-TNF biologic, etanercept was not associated with a statistically significant or clinically meaningful difference in HAQ scores, MD: 0.13 (95% CrI -0.40 to 0.66).
   b. biologic alone without MTX: Compared to monoclonal TNF antibody biologic, etanercept was not associated with a statistically significant or clinically meaningful difference in HAQ scores, MD: 0.30 (95% CrI -0.61 to 1.20).
3. Biologic dose, SD versus LD versus HD biologic:
   a. biologic + MTX: compared to SD biologic, LD biologic was not associated with any statistically significant difference in HAQ scores, MD: -0.06 (95% CrI -0.45 to 0.33). HD biologic was not associated with any statistically significant or clinically meaningful difference in HAQ scores compared to SD biologic, MD: 0.20 (95% CrI -0.20 to 0.60) and LD biologic, MD: 0.26 (95% CrI -0.29 to 0.80).
   b. biologic alone without MTX: There were no studies to perform this analysis.

Main analyses using NMA

Fourteen studies (eleven 2-arm and three 3-arm trials) with 4172 participants provided HAQ data in MTX-naive participants (Appendix 8). Compared to MTX, SD adalimumab + MTX was associated with statistically significantly better HAQ score, the mean difference being -0.30 (95% CI -0.59 to -0.02), which was also clinically meaningful.

Subgroup analyses by RA disease duration (early versus established versus late RA)

Early RA (RA disease duration less than two years)

Four 2-arm and two 3-arm trials provided HAQ data. There were no statistically significant differences between various treatments (2,068 participants, 6 studies) (Appendix 9).

Established RA (disease duration 2 to 10 years)

Six 2-arm and one 3-arm trial provided HAQ data. There were no statistically significant differences between various treatments (2,078 participants, 7 studies) (Appendix 10).

Late RA (disease duration more than 10 years)

There were not enough data to perform NMA.

Subgroup analyses by trial duration

Trial duration, six months or less

All studies that provided HAQ data were two-arm trials. There were no statistically significant differences between various treatments (243 participants, 4 studies) (Appendix 11).

Trial duration, between six and 12 months

Five 2-arm and one 3-arm trials provided HAQ data. There were no statistically significant differences between various treatments (2214 participants, 6 trials) (Appendix 12).

Trial duration, between six and 12 months

Two 2-arm and two 3-arm trials provided HAQ data. There were no statistically significant differences between various treatments (1715 participants, 4 studies) (Appendix 13).

Primary/major benefit outcome: Remission

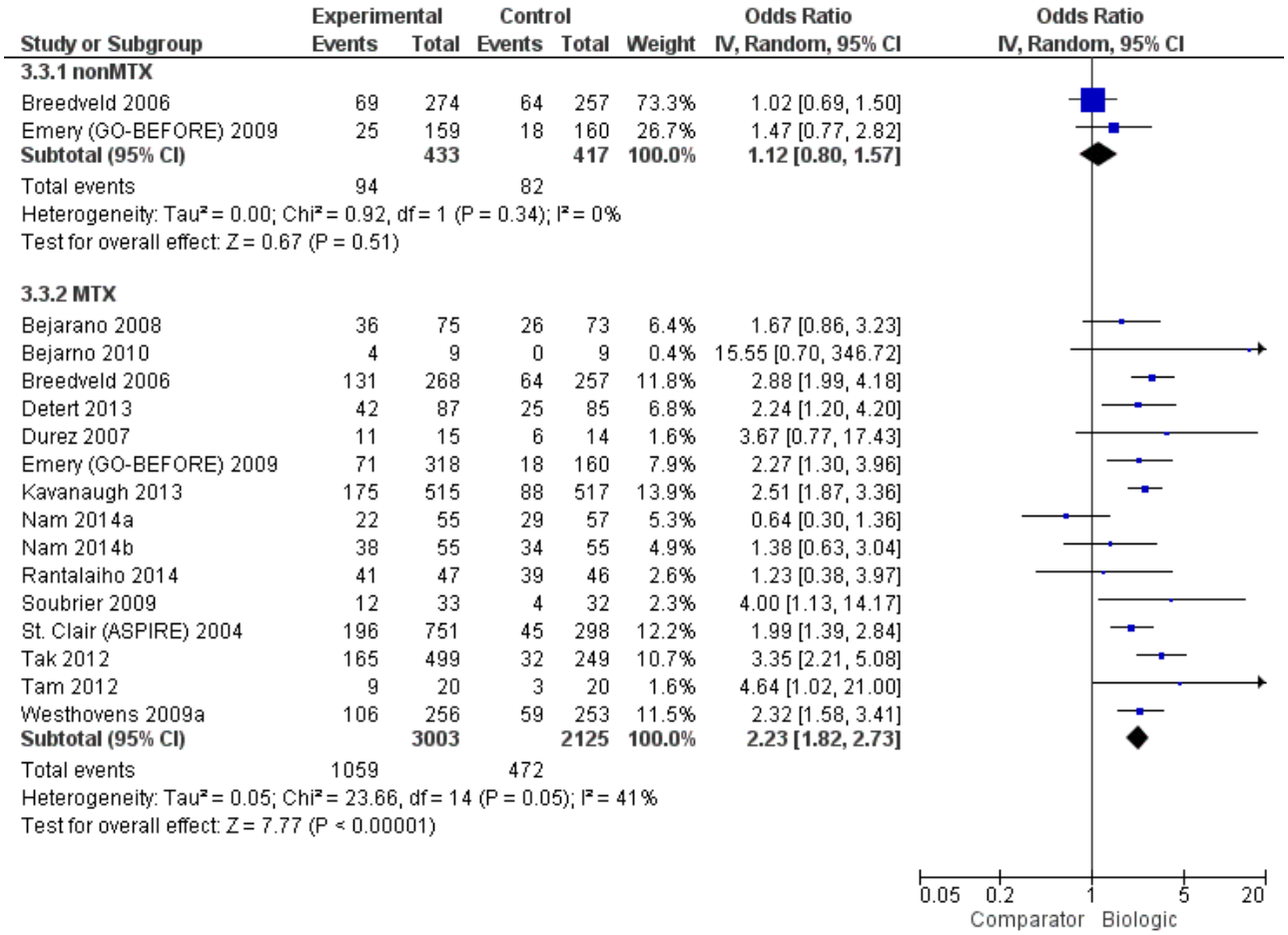
Fifteen studies with 5561 participants reported data on remission (defined as DAS less than 1.6 or DAS28 less than 2.6). Of these, all studies included at least one arm with participants on a biologic with concomitant MTX.

Odds ratios using standard meta-analysis

Biologic + MTX versus active comparator

The odds of remission with biologic + MTX was statistically significantly and clinically meaningfully higher, OR 2.23 (95% CI 1.82 to 2.73), absolute difference 15% (95% CI 11% to 19%), NNTB = 5 (95% CI 6 to 7); I^2 of 41%, indicating moderate heterogeneity (Figure 5) (moderate-quality evidence)

Figure 5. Remission: biologic (with and without concomitant MTX) versus comparator



Biologic without MTX versus active comparator

There was no evidence of a statistically significantly and clinically meaningfully difference, OR 1.12 (95% CI 0.08 to 1.57), absolute difference 2% (95% CI -3% to 8%), I^2 of 0%, indicating heterogeneity that might not be important (Figure 5) (moderate-quality evidence).

Odds ratios by biologic type and dose using NMA

The odds ratios (95% CrI) of remission by the type of biologic and the dose were as follows (5561 participants, 15 studies).

1. Type of biologic, TNF versus non-TNF biologic:
   a. biologic + MTX: compared to non-TNF biologic + MTX, TNF biologic + MTX was not associated with any statistically significant or clinically meaningful difference in the odds of remission, OR: 1.30 (95% CrI 0.79 to 2.19);
   b. biologic alone without MTX: there were no data to perform this analysis.
2. Type of biologic, etanercept versus TNF antibody biologic versus non-TNF biologic:
   a. biologic + MTX: compared to monoclonal antibody TNF biologic, monoclonal antibody TNF biologic + MTX was not associated with any statistically significant or clinically meaningful difference in the odds of remission, OR: 1.26 (95% CrI 0.76 to 2.15). There were no statistically significant or clinically meaningful differences between etanercept + MTX and monoclonal antibody TNF biologic + MTX, OR: 0.62 (95% CrI 0.24 to 1.67);
   b. biologic alone without MTX: there were no data to perform this analysis.
3. Biologic dose, SD versus LD versus HD biologic:
   a. biologic + MTX: compared to SD biologic monotherapy, HD biologic and LD biologic monotherapy were associated with no statistically significant or clinically meaningful difference in odds of remission, OR: 1.13 (95% CrI 0.68 to 1.78) and OR: 1.29 (95% CrI 0.69 to 2.50).
   b. biologic alone without MTX: compared to SD biologic, HD biologic was associated with no statistically significant or clinically meaningful difference in odds of remission, OR: 1.72 (95% CrI 0.65 to 4.38).

Main analyses using NMA

Fifteen studies (eleven 2-arm, three 3-arm, and one 4-arm trial) with 5561 participants provided remission data in MTX-naive participants (Appendix 14). Compared to MTX, several biologics were associated with higher odds of disease remission:

1. SD infliximab + MTX, OR 1.82;
2. SD adalimumab + MTX, OR 2.55;
3. SD abatacept intravenous + MTX, OR 2.33;
4. SD golimumab subcutaneous + MTX, OR 2.69;

5. SD rituximab + MTX, OR 3.22;
6. LD rituximab + MTX, OR 3.55;
7. HD infliximab + MTX, OR 2.80.

Compared to SD abatacept subcutaneous, the following combinations with MTX were each associated with higher odds of RA disease remission:

1. SD adalimumab + MTX, OR 2.69;
2. SD golimumab, OR 2.85;
3. SD rituximab + MTX, OR 3.40;
4. LD rituximab + MTX, OR 3.75;
5. HD infliximab + MTX, OR 2.96.

Subgroup analyses by RA disease duration (early versus established versus late RA)

Early RA (RA disease duration less than two years)

There were five 2-arm and three 3-arm trials. Compared to MTX + placebo, SD rituximab + MTX and LD rituximab + MTX were associated with statistically significantly higher odds of remission, OR: 3.20 (95% CrI 1.24 to 8.66) and OR: 3.54 (95% CrI 1.35 to 9.45), respectively (2313 participants, 7 studies) (Appendix 15).

Established RA (disease duration 2 to 10 years)

There were six 2-arm trials and one each of 3-arm and 4-arm trials. Compared to MTX + placebo, SD infliximab + MTX, SD adalimumab + MTX, SD abatacept + MTX and SD golimumab + MTX were associated with statistically significantly higher odds of remission, with ORs ranging from 2.32 to 7.01 (3248 participants, 8 studies) (Appendix 16).

Late RA (disease duration more than 10 years)

There were no studies for late RA.

Subgroup analyses by trial duration

Trial duration, six months or less

There were five 2-arm trials and one 4-arm trial. Compared to MTX + placebo, the following were associated with higher odds of remission: methylprednisolone + MTX, OR: 8.44; SD adalimumab + MTX, OR: 2.67; and SD golimumab + MTX, OR: 2.70 (2058 participants, 6 studies) (Appendix 17).

Trial duration, between six and 12 months

There were three 2-arm trials and one 3-arm trial. None of the comparisons were statistically significant (1697 participants, 4 studies) (Appendix 18).

Trial duration, between six and 12 months

There were three 2-arm and two 3-arm trials. Compared to MTX, SD rituximab + MTX and LD rituximab + MTX were associated with higher odds of remission, ORs ranging from 2.42 to 3.55. Compared to SD adalimumab, SD adalimumab + MTX and LD rituximab + MTX were associated with higher odds of remission, OR: 2.63 and 3.85, respectively (1806 participants, 5 studies) (Appendix 19).

Primary/major benefit outcome: Radiographic progression

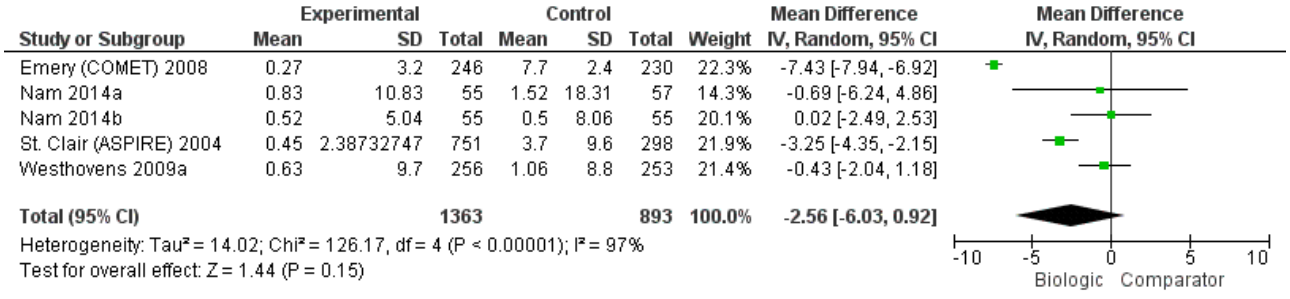
Five studies with 2256 participants reported data on radiographic progression. Of these, all studies had at least one arm with participants on a biologic with concomitant MTX.

Odds ratios using standard meta-analyses

Biologic + MTX versus active comparator

The use of biologic + MTX therapy was not statistically significantly associated with less radiographic progression compared to MTX with a mean difference of -2.56 (95% CI -6.03 to 0.92) Sharp or modified Sharp units (0 to 448 points), absolute difference -0.57% (95% CI -1.35% to 0.21%) (Figure 6) with a considerable degree of heterogeneity, with I^2 of 97%.; this change was not clinically meaningful (low-quality evidence).

Figure 6. Radiographic progression: biologic (+MTX) versus comparator



Biologic without MTX versus active comparator

There were no studies of biologic therapy without MTX.

Odds ratios by biologic type and dose using NMA

The overall radiographic progression by the type of biologic and the dose was as follows (2256 participants, 5 studies).

1. Type of biologic, TNF versus non-TNF biologic:
   a. biologic + MTX: compared to TNF biologic + MTX, non-TNF biologic + MTX was associated with no statistically significant or clinically meaningful difference in radiographic progression, MD: 3.32 (95% CrI -1.08 to 7.63);
   b. biologic alone without MTX: there were no data to perform this analysis.
2. Type of biologic, etanercept versus TNF antibody biologic versus non-TNF biologic:
   a. biologic + MTX: compared to etanercept + MTX, monoclonal antibody + MTX or non-TNF biologic + MTX were not associated with any statistically significant or clinically

meaningful difference in radiographic progression, MD: 1.87 (95% CrI -2.34 to 6.05) and MD: 4.10 (95% CrI -0.64 to 8.68);

b. biologic alone without MTX: there were no data to perform this analysis.

3. Biologic dose, SD versus LD versus HD biologic:
   a. biologic + MTX: compared to SD biologic + MTX, LD biologic + MTX, MD: -0.05 (95% CrI -3.34 to 3.20) was not associated with statistically significant or clinically meaningful difference in radiographic progression;
   b. biologic alone without MTX: there were no data to perform this analysis.

Main analyses using NMA

None of the biologics were statistically significantly different from each other or DMARDs (Appendix 20).

Subgroup analyses by RA disease duration (early versus established versus late RA)

Early RA (RA disease duration less than two years)

There were not enough data to perform NMA.

Established RA (disease duration 2 to 10 years)

There were not enough data to perform NMA.

Late RA (disease duration more than 10 years)

There were not enough data to perform NMA.

Subgroup analyses by trial duration

Trial duration, six months or less

There were not enough data to perform NMA.

Trial duration, between six and 12 months

Three 2-arm trials and one 3-arm trials provided data. Compared to MTX + placebo, three treatments were associated with slower radiographic progression that was statistically significant with a mean difference of:

1. SD etanercept + MTX, MD: -5.50 (95% CrI -7.09 to -3.82);
2. SD infliximab + MTX, MD: -3.30 (95% CrI -5.46 to -1.15); and
3. HD infliximab + MTX, MD: -3.20 (95% CrI -5.35 to -1.06)

(2144 participants, 4 studies) (Appendix 21).

Trial duration, between six and 12 months

There were not enough data to perform NMA.

Primary/major harm outcome: Withdrawals due to adverse events

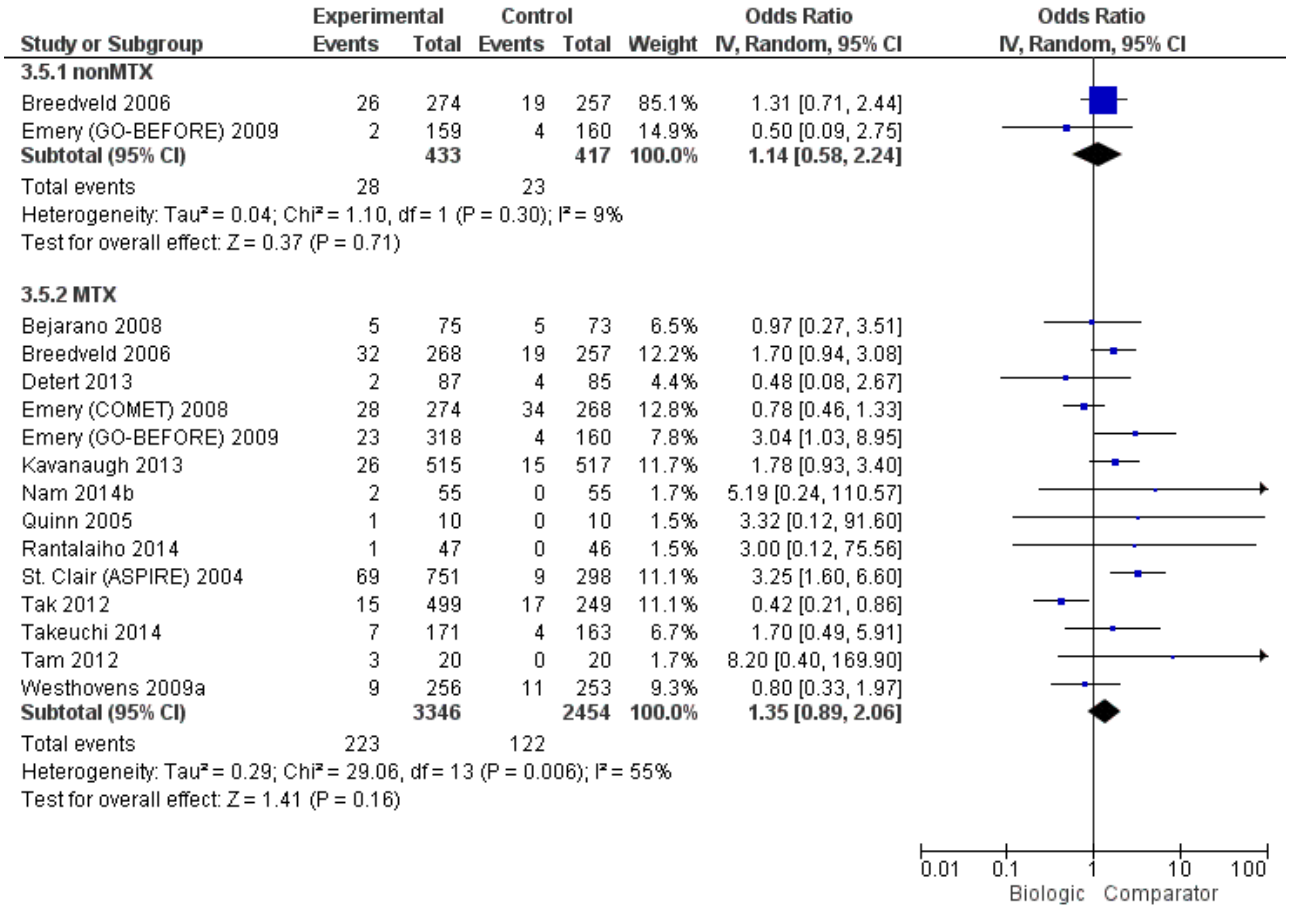
Fourteen studies with 6233 participants reported withdrawals due to adverse events (AE). Of these, all studies included at least one arm with participants on a biologic with concomitant MTX.

Odds ratios using standard meta-analyses

Biologic + MTX versus active comparator

Results were inconclusive for a statistically significantly or clinically meaningfully difference in withdrawals due to AEs with biologic + MTX compared to MTX with an OR: 1.35 (95% CI 0.89 to 2.06; where the 95% confidence interval includes possibility of important harm), absolute difference 2% (95% CI 0% to 4%), I^2 of 55%, representing moderate to substantial heterogeneity; Figure 7 (low-quality evidence).

Figure 7. Withdrawals due to adverse events: biologic (with and without concomitant MTX) versus comparator



Biologic + MTX versus active comparator

Results were inconclusive for a statistically significantly and clinically meaningfully difference in withdrawals due to AEs in the biologic without MTX compared to MTX, OR: 1.14 (95% CI 0.58 to 2.24), absolute difference (95% CI 0% (-4% to 4%), with a I^2 of 9%, representing heterogeneity that might not be important. Figure 7 (low-quality evidence).

Odds ratios by biologic type and dose using NMA

Overall withdrawals due to AEs differed by the type of biologic and the dose as follows (6233 participants, 14 trials).

1. Type of biologic, TNF versus non-TNF biologic:
   a. biologic + MTX: compared to TNF biologic, non-TNF biologic showed clinically meaningfully and statistically significantly lower odds of withdrawals due to AEs, OR: 0.32 (95% CrI 0.12 to 0.80);
   b. biologic alone without MTX: there were no studies to compare.
2. Type of biologic, etanercept versus TNF antibody biologic versus non-TNF biologic:
   a. biologic + MTX: compared to monoclonal antibodies against TNF, non-TNF biologic was associated with clinically meaningful and statistically significantly lower odds of withdrawals due to AEs, OR: 0.27 (95% CrI 0.12 to 0.61), except for etanercept, OR: 0.44 (95% CrI 0.20 to 1.14). We also found compared to TNF biologic, non-TNF biologic was not associated with any statistically significant or clinically meaningful difference in odds of withdrawals due to AEs, OR: 1.66 (95% CrI 0.60 to 5.02);
   b. biologic alone without MTX: there were no studies to compare.
3. Biologic dose, SD versus LD versus HD biologic:
   a. biologic + MTX: compared to SD biologic, odds of withdrawal due to AEs with HD or LD biologic were not statistically significantly or clinically meaningfully different from SD biologic (HD: OR: 1.41 (95% CrI 0.94 to 2.12), LD: OR: 0.56 (95% CrI 0.23 to 1.24) However, compared to HD biologic, LD biologic was associated with a statistically significant and clinically meaningful lower odds of withdrawals due to AEs, OR: 0.40 (95% CrI 0.15 to 0.97);
   b. biologic alone without MTX: compared to HD biologic, LD biologic was associated with a statistically significant and clinically meaningful lower odds of withdrawals due to AEs, OR: 0.22 (95% CrI 0.03 to 0.92), although data for this analysis were sparse.

Main analyses using NMA

Compared to MTX, SD adalimumab + MTX, SD infliximab + MTX, HD golimumab + MTX, and HD infliximab + MTX, were associated with higher odds of withdrawals due to AEs, with ORs ranging 1.74 to 3.68. Compared to SD rituximab + MTX, HD golimumab + MTX

and HD infliximab + MTX were associated with higher OR of 9.97 and 6.51. Compared to LD rituximab + MTX, HD golimumab + MTX and HD infliximab + MTX were associated with higher OR of 8.45 and 5.57. Compared to HD golimumab, HD golimumab + MTX was associated with higher odds, 8.13 (95% CrI 1.80 to 67.37) (6233 participants, 14 studies) (Appendix 22).

Subgroup analyses by RA disease duration (early versus established versus late RA)

Early RA (RA disease duration less than two years)

There were four 2-arm, and two 3-arm trials. Compared to MTX + placebo, both SD infliximab + MTX and HD infliximab + MTX were associated with higher odds of withdrawals due to AEs, OR: 3.34 and OR: 3.38, respectively. Compared to SD infliximab + MTX, SD rituximab + MTX and LD rituximab + MTX were associated with lower odds of withdrawals due to AEs, OR: 0.11 and OR: 0.13, respectively (2416 participants, 6 trials) (Appendix 23).

Established RA (disease duration 2 to 10 years)

There were four 2-arm, one 3-arm and one 4-arm trials. HD golimumab subcutaneous was associated with statistically significantly higher odds of withdrawals due to AEs compared with MTX + placebo, OR: 3.78; SD etanercept + MTX, OR: 4.84; and HD golimumab subcutaneous, OR: 8.17 (3667 participants, 6 trials) (Appendix 24).

Late RA (disease duration more than 10 years)

There were not enough data to perform NMA.

Subgroup analyses by trial duration

Trial duration, six months or less

There were three 2-arm trials and one 4-arm trial. Compared to MTX + placebo, HD golimumab subcutaneous + MTX was associated with 3.71-times higher odds of withdrawals due to AEs. Compared to HD golimumab subcutaneous monotherapy, HD golimumab subcutaneous + MTX was associated with 8.06-times higher odds of withdrawals due to AEs (2175 participants, 4 trials) (Appendix 25).

Trial duration, between six and 12 months

There were four 2-arm and two 3-arm trials. Compared to MTX + placebo, both SD infliximab + MTX and HD infliximab + MTX were associated with higher odds of withdrawals due to AEs, OR: 3.32 and OR: 3.36, respectively (3029 participants, 6 trials) (Appendix 26).

Trial duration, between six and 12 months

There were no data.

Primary/major harm outcome: Serious adverse events

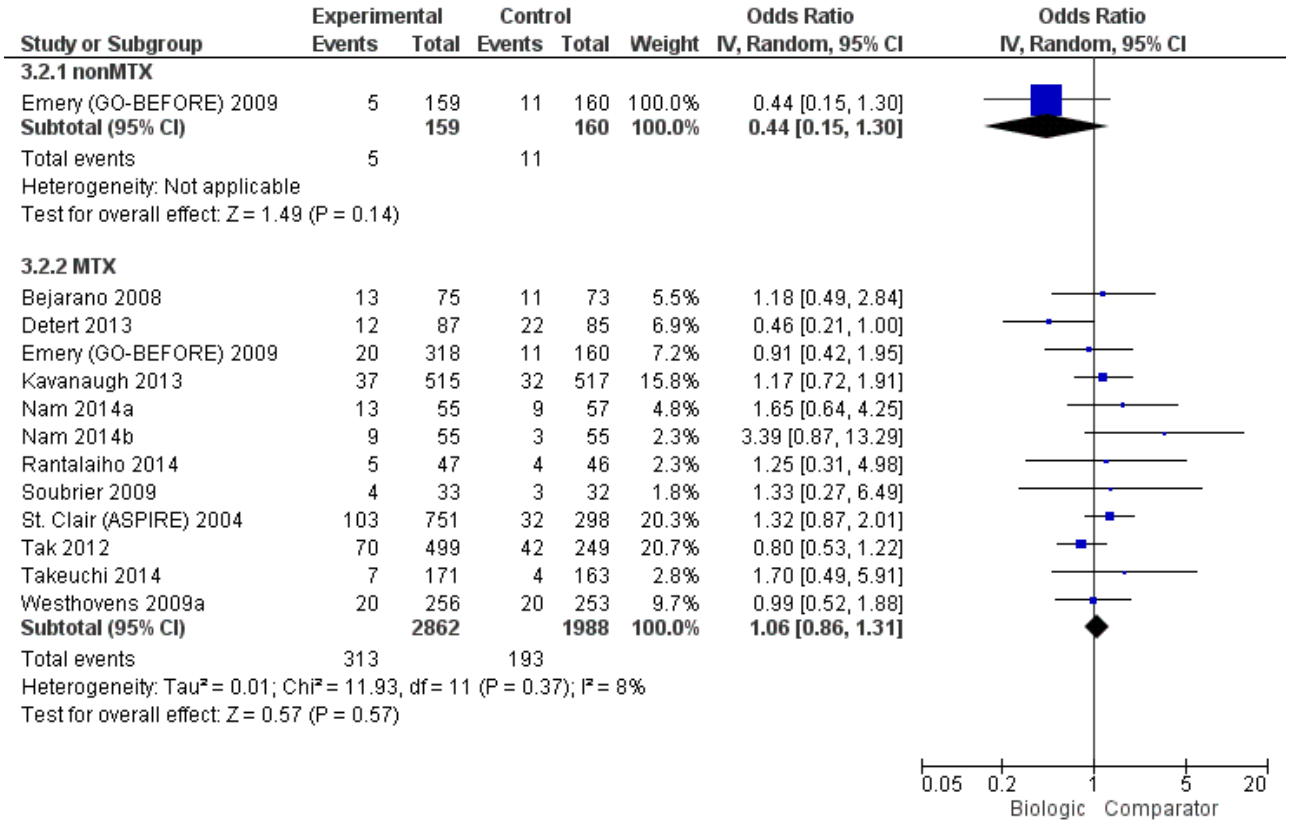
Twelve studies with 5169 participants reported serious adverse events (SAEs). Of these, all studies included at least one arm with participants on a biologic with concomitant MTX.

Odds ratios using standard meta-analyses

Biologic + MTX versus active comparator

The use of biologic + MTX therapy was associated with no evidence of a statistically significant or clinically meaningful difference in the odds of SAEs versus MTX, OR: 1.06 (95% CI 0.86 to 1.31), absolute difference 1% (95% CI -1% to 3%), I^2 of 8%, representing heterogeneity which might not be important (Figure 8) (moderate-quality evidence).

Figure 8. Serious adverse events: biologic (with and without concomitant MTX) versus comparator



Biologic without MTX versus active comparator

The use of biologic without MTX therapy was associated with no evidence of a statistically significant or clinically meaningful difference in the odds of SAEs versus MTX (based on one study), OR: 0.44 (95% CI 0.15 to 1.30) absolute difference -4% (95% CI -8% to 1%), with no I^2, since data were derived from one study (low-quality evidence).

Odds ratios by biologic type and dose using NMA

The overall SAEs differed by the type of biologic and the dose as follows (5009 participants, 12 studies).

1. Type of biologic, TNF versus non-TNF biologic:
   a. biologic + MTX: compared to TNF biologic, the odds of SAEs were not statistically significantly or clinically meaningfully different with non-TNF biologic, OR: 0.73 (95% CrI 0.42 to 1.28);
   b. biologic alone without MTX: there were no studies comparing biologic monotherapy regimens to each other.
2. Type of biologic, etanercept versus TNF antibody biologic versus non-TNF biologic:
   a. biologic + MTX: the odds of SAEs were not statistically significantly or clinically meaningfully different with the comparators as follows: non-TNF biologic, OR: 0.77 (95% CrI 0.45 to 1.34) and etanercept, OR: 3.40 (95% CrI 0.82 to 18.68). Compared to MTX + non-TNF biologic, MTX + TNF biologic was associated with statistically significantly higher odds of SAEs, OR: 4.41 (95% CrI 1.01 to 25.18), which may be clinically meaningful;
   b. biologic alone without MTX: there were no studies comparing biologic monotherapies to each other.
3. biologic dose, SD versus LD versus HD biologic:
   a. biologic + MTX: the odds of SAEs were not statistically significantly or clinically meaningfully different of the following compared to SD biologic as follows: HD biologic, OR: 1.02 (95% CrI 0.65 to 1.61); and LD biologic, OR: 0.94 (95% CrI 0.53 to 1.67);
   b. biologic alone without MTX: there were no studies comparing biologic monotherapies to each other by dose.

Main analyses using NMA

Twelve RCTs (nine 2-arm, two 3-arm, and one 4-arm trial) enrolling 5009 participants (Appendix 27) provided data for all dose analyses for SAEs. None of the biologics were significantly different from each other or MTX, except that HD golimumab was associated with lower odds of SAEs compared to SD etanercept + MTX.

Subgroup analyses by RA disease duration (early versus established versus late RA)

Early RA (RA disease duration less than two years)

There were five 2-arm and two 3-arm trials. There were no statistically significant differences between biologic and comparators or between biologic + MTX and comparators (MTX + placebo in most cases) (2618 participants, 7 studies) (Appendix 28).

Established RA (disease duration 2 to 10 years)

There were four 2-arm and one 4-arm trial. There were no statistically significant differences between biologic and comparators or between biologic + MTX and comparators (MTX + placebo in most cases) (2391 participants, 5 studies) (Appendix 29).

Late RA (disease duration more than 10 years)

There were no data to analyze.

Subgroup analyses by trial duration

Trial duration, six months or less

There were four 2-arm and one 4-arm trial. There were no statistically significant differences between biologic and comparators or between biologic + MTX and comparators (MTX + placebo in most cases) (2240 participants, 5 studies) (Appendix 30).

Trial duration, between six and 12 months

There were two 2-arm and one 3-arm trial. There were no statistically significant differences between biologic and comparators or between biologic + MTX and comparators (1668 participants, 3 studies) (Appendix 31).

Trial duration, between six and 12 months

There were two 2-arm and one 3-arm trial. There were no statistically significant differences (989 participants, 3 studies) (Appendix 32).

Primary/major harm outcome: Cancer

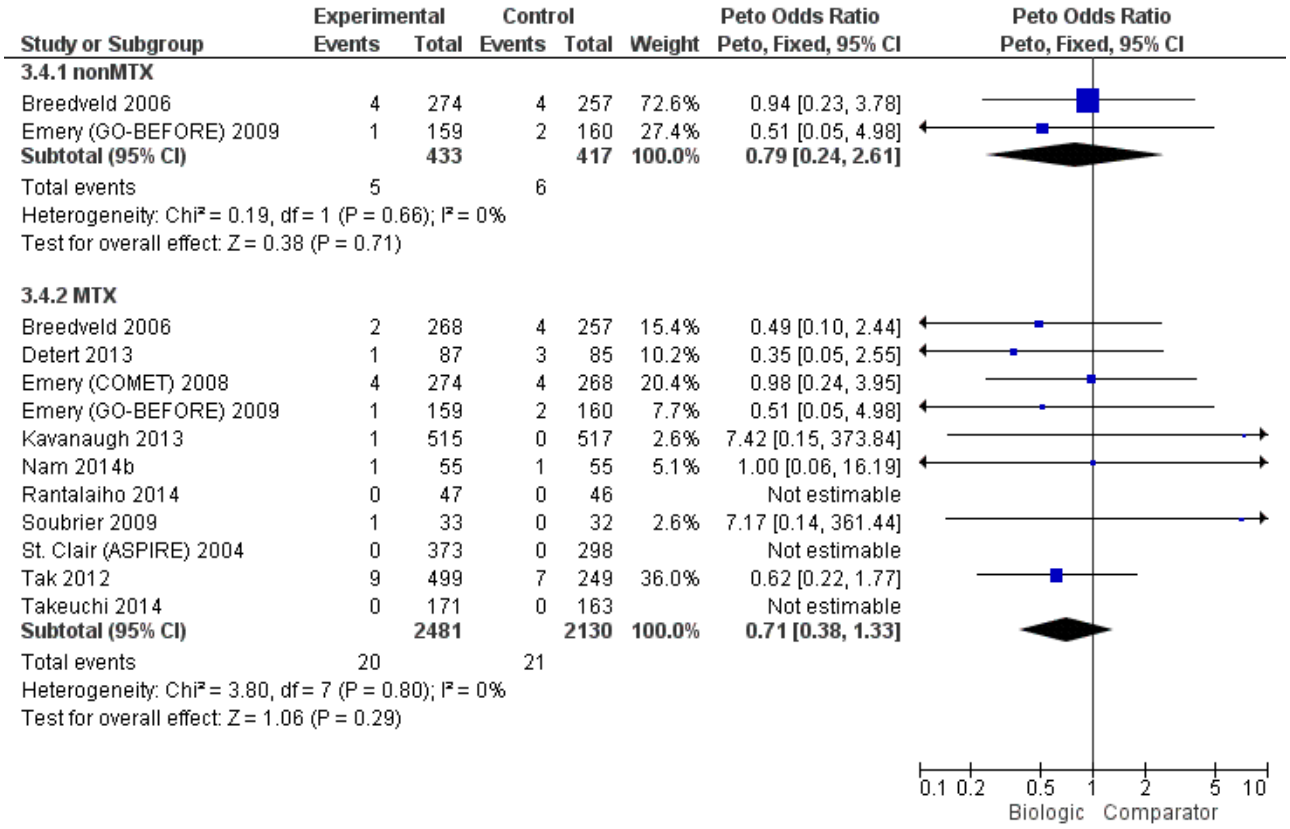
Eleven studies with 5044 participants reported cancer. Of these, all studies included at least one arm with participants on a biologic with concomitant MTX.

Odds ratios using standard meta-analyses

Biologic + MTX versus active comparator

The use of biologic + MTX therapy was inconclusive for evidence of a statistically significant or clinically meaningful difference in the odds of cancer, compared to MTX, Peto OR: 0.71 (95% CI 0.38 to 1.33), absolute difference 0% (95% CI 0% to 0%) with an I^2 of 0% representing no heterogeneity (Figure 9) (low-quality evidence).

Figure 9. Cancer: biologic (with and without concomitant MTX) versus comparator



Biologic without MTX versus active comparator

The use of biologic without MTX therapy was inconclusive for evidence of a statistically significant or clinically meaningful difference in the odds of cancer, compared to MTX, Peto OR: 0.79 (95% CI 0.24 to 2.61), absolute difference 0% (95% CI -2% to 1%) with an I^2 of 0%, representing no heterogeneity (Figure 9) (low-quality evidence).

Odds ratios by biologic type and dose using NMA

The overall rate of cancer by the type of biologic and the dose were as follows (5044 participants, 11 studies).

1. Type of biologic, TNF versus non-TNF biologic:
   a. biologic + MTX: compared to TNF inhibitors, the odds of cancer with non-TNF biologic were not statistically

significantly or clinically meaningfully different, Peto OR: 0.80 (95% CrI 0.20 to 3.28);

b. biologic alone without MTX: no comparisons were available.

2. Type of biologic, etanercept versus TNF antibody biologic versus non-TNF biologic:
   a. biologic + MTX: compared to monoclonal TNF antibodies, the odds of cancer were not statistically significantly or clinically meaningfully different with etanercept, Peto OR: 1.43 (95% CrI 0.25 to 8.68) or non-TNF biologic, Peto OR: 0.90 (95% CrI 0.20 to 4.33);
   b. biologic alone without MTX: no comparisons were available.
3. Biologic dose, SD versus LD versus HD biologic:
   a. biologic + MTX: compared to SD biologic + MTX, the odds of cancer were not statistically significantly or clinically meaningfully different with LD biologic + MTX, Peto OR: 1.50 (95% CrI 0.42 to 5.07). No comparisons were available for HD biologic + MTX versus SD biologic + MTX;
   b. biologic alone without MTX: compared to SD biologic, the odds of cancer were not statistically significantly or clinically meaningfully different with HD biologic, Peto OR: 0.41 (95% CrI 0.01 to 6.10). No comparisons were available for LD biologic versus SD biologic.

Main analyses using NMA

Eleven RCTs (eight 2-arm and three 3-arm trials) enrolling 5044 participants (Appendix 33): we found no statistically significant differences comparing various biologics to MTX or to each other.

Subgroup analyses by RA disease duration (early versus established versus late RA)

Early RA (RA disease duration less than two years)

There were not enough data to perform NMA.

Established RA (disease duration 2 to 10 years)

No statistically significant differences in cancer rates were noted between treatments.

Late RA (disease duration more than 10 years)

There were not enough data to perform NMA.

Subgroup analyses by trial duration

Trial duration, six months or less

No statistically significant differences in cancer rates were noted between treatments (2081 participants, 5 studies (four 2-arm and one 3-arm trial)) (Appendix 35).

Trial duration, between six and 12 months

There were not enough data to perform NMA.

Trial duration, more than 12 months

There were not enough data to perform NMA.

Summary of safety warnings from regulatory agencies

Evidence from RCTs is limited in informing participants and physicians about uncommon or rare adverse events. In Appendix 36, we summarize warnings from the FDA, EMA and Health Canada, the regulatory agencies in the USA, Europe and Canada, respectively.

DISCUSSION

Summary of main results

ACR50

In standard meta-analysis, based on moderate-quality evidence, biologic use + MTX was associated with a statistically significant and clinically meaningful higher odds of ACR50 compared to MTX with an odds ratio of 1.95 (95% CI 1.71 to 2.23) or a RR of 1.40 (95% CI 1.30 to 1.49), absolute difference 16% (95% CI 13% to 20%) and NNTB = 7 (95% CI 6 to 8). TNF biologic monotherapy did not show a clinically meaningful or statistically significant difference from MTX (there were no data for non-TNF monotherapy). Results were similar in the NMA.

In standard meta-analysis, based on high-quality evidence, biologic + MTX was also associated with statistically significant and clinically meaningful higher odds of ACR50 compared to the comparator in both TNF biologic and non-TNF biologic subgroups with RR of 1.44 (95% CI 1.34 to 1.54) and 1.27 (95% CI 1.14 to 1.42) and absolute difference 17% (95% CI 13% to 21%) and 13% (95% CI 7% to 19%), and NNTB = 6 (95% CI 5 to 8) and = 8 (95% CI 6 to 14), respectively. Results were similar for the NMA.

In subgroup analyses using the NMA, with respect to the type of biologics and biologics by dose, TNF biologics did not show evidence of a statistically significant or clinically meaningful difference from non-TNF biologics and similar results were seen when comparing biologics doses.

Function assessed by HAQ

In standard meta-analysis, there was moderate-quality evidence that biologics use + MTX was associated with statistically significant HAQ score improvement with a mean difference of -0.10 (95% CI -0.16 to -0.04) and an absolute difference of -3.3% (95% CI -5.3% to -1.3%) when compared to MTX, but the difference did not seem to be clinically meaningful. TNF biologic monotherapy did not show a statistically significant or clinically meaningful difference from MTX (there were no data for non-TNF monotherapy). Results were similar in the NMA.

In standard meta-analysis, based on low-quality evidence, compared to MTX, TNF biologic + MTX was associated with lower HAQ scores with better HAQ score improvement with mean difference of -0.09 (95% CI -0.26 to 0.07), which was neither statistically significant nor clinically meaningful. Based on moderate-quality evidence, non-TNF biologic + MTX was associated with better HAQ scores with statistically significant and clinically meaningful HAQ score improvement with a mean difference of -0.22 (95% CI -0.26 to -0.18) and an absolute difference of -7.3% (95% CI -8.7% to -6%) compared to MTX. Results did not show evidence of a clinically meaningful or statistically significant difference in TNF biologic monotherapy versus MTX.

In NMA, none of the subgroups (TNF or non-TNF biologic) showed statistically significant or clinically meaningful differences. We noted no evidence of clinically meaningful and statistically significant differences in HAQ scores by the type of biologic (TNF versus non-TNF biologics or receptor versus antibody TNF biologic) or in biologic-dose analysis.

Remission

In standard meta-analysis, based on moderate-quality evidence, biologic use + MTX was associated with a statistically significant and clinically meaningful higher odds of remission compared to MTX, with OR of 2.23 (95% CI 1.82 to 2.73) or a RR of 1.62 (95% CI 1.33 to 1.98), absolute difference 15% (95% CI 11% to 19%) and NNTB = 5 (95% CI 6 to 7). TNF biologic monotherapy did not show evidence of a statistically significant or clinically meaningful difference from MTX (there were no data for non-TNF monotherapy). Results were similar in the NMA.

In standard meta-analysis, based on moderate-quality evidence, TNF biologic + MTX showed a statistically significant and clinically meaningful higher rate of remission with risk ratio of 1.55 (95% CI 1.22 to 1.96) and absolute difference 14% (95% CI 9% to 19%) and NNTB = 7 (95% CI 5 to 10), as did non-TNF biologic + MTX with RR 2.10 (95% CI 1.45 to 3.04), absolute difference 19% (95% CI 15% to 24%) and NNTB = 6 (95% CI 4 to 9). Results were similar in the NMA.

In subgroup analyses using the NMA, there was no evidence of statistically significant or clinically meaningful differences among biologic groups or in biologic-dose analysis.

Radiographic progression

In standard meta-analysis, based on low-quality evidence, biologic use + MTX showed a non-statistically significant difference in radiographic progression versus MTX with a mean difference of -2.56 (95% CI -6.03 to 0.92) and absolute difference -0.57% (95% CI -1.35% to 0.21%) on a scale of 0 to 448 points; this difference does not seem to be clinically meaningful. There were no data for TNF-biologic or non-TNF biologic monotherapy.

In standard meta-analysis, based on low-quality evidence, TNF biologic + MTX showed a non-statistically significant improvement in radiographic progression versus MTX with mean difference of -3.18 (95% CI -6.80 to 0.43), absolute difference -0.71% (95% CI -1.52% to 959%). In NMA, this comparison was statistically significant with a mean difference of -3.73 (95% CrI -5.78 to -1.62), absolute difference -0.83% (95% CI -1.29% to -0.36%) and NNTB = 3 (95%CI, 3 to 7), but the clinical significance of this difference was unclear. Non-TNF biologic + MTX showed a much lower non-statistically significant improvement with a mean difference of -0.43 (95% CI -2.04 to 1.18), absolute difference -0.22% (95% CI -0.46% to 0.26%), which was also not significantly different in the NMA.

In subgroup NMA, no evidence of clinically meaningful or statistically significant differences were noted by the type of biologic (TNF versus non-TNF biologic), receptor versus antibody TNF biologic, or biologic dose (SD versus HD versus LD).

Withdrawals due to adverse events

In standard meta-analysis, based on low-quality evidence, results were inconclusive for biologic use + MTX for any clinically meaningful or statistically significant difference in withdrawal due to adverse events rates compared to MTX, since the 95% CI included the possibility of important harm with an OR of 1.35 (95% CI 0.89 to 2.06) or a RR of 1.32 (95% CI 0.89 to 1.97) and absolute difference of 2% (95% CI 0% to 4%). Results were inconclusive for TNF biologic monotherapy versus MTX (there were no data for non-TNF monotherapy). Results were similar in the NMA.

In standard meta-analysis, based on moderate-quality evidence, there was a clinically meaningful and statistically significant increase in withdrawals due to adverse events in TNF biologic + MTX versus MTX with a RR of 1.60 (95% CI 1.10 to 2.32), absolute difference 3% (95% CI 1% to 4%) and NNTH = 35 (95% CI 17 to 183). Based on low-quality evidence, there was no evidence of a clinically meaningful and statistically significant difference in this outcome among the non-TNF biologic + MTX versus MTX, RR of 0.56 (95% CI 0.31 to 1.01), absolute difference -2% (95% CI -5% to 1%). Results were similar in the NMA.

In subgroup analyses using the NMA, compared to TNF biologic, non-TNF biologic showed a clinically meaningful and statistically significant lower odds ratio of withdrawals due to adverse events, OR 0.32 (95% CrI 0.12 to 0.80). Compared to HD biologic with concomitant MTX, LD biologic with concomitant MTX was associated with statistically significantly lower withdrawals due to adverse events, OR: 0.40 (95% CrI 0.15 to 0.97), which also seemed to be clinically meaningful.

Serious adverse events (SAEs)

In standard meta-analysis, based on moderate-quality evidence, the odds of SAEs did not show evidence of a statistically significant or clinically meaningful difference in participants comparing biologics + MTX to MTX alone; OR was 1.06 (95% CI 0.86 to 1.31), RR was 1.05 (95% CI 0.87 to 1.26) and absolute difference of 1% (95% CI -1% to 3%). Based on low-quality evidence, TNF biologic monotherapy did not show evidence of a clinically meaningful or statistically significant difference from MTX (there were no data for non-TNF monotherapy). Results were similar in the NMA.

In standard meta-analysis, based on moderate-quality evidence, there was no evidence of a statistically significant or clinically meaningful difference in the TNF biologic + MTX versus MTX with a RR of 1.14 (95% CI 0.92 to 1.42), absolute difference 1% (95% CI -1% to 3%). Based on low-quality evidence, there was no evidence of a clinically meaningful and statistically significant difference in the non-TNF biologic + MTX versus MTX with a RR of 0.87 (95% CI 0.64 to 1.18), absolute difference -1% (95% CI -5% to 2%).

In subgroup NMA, in one comparison TNF biologic + MTX was associated with statistically significantly higher odds of SAEs compared to non-TNF biologic + MTX, with OR of 4.41 (95% CrI 1.01 to 25.18), which may be clinically meaningful. Other subgroup comparisons did not show evidence of a clinically meaningful or statistically significant difference.

Cancer

In standard meta-analysis, based on low-quality evidence, results were inconclusive for the risk of cancer for statistically significant or clinically meaningful difference for biologic + MTX versus MTX with a Peto's OR of 0.71 (95% CI 0.38 to 1.33) and an absolute difference of 0% (95% CI 0% to 0%). Results were also inconclusive for TNF biologic monotherapy versus MTX (there were no data for non-TNF monotherapy). Results were similar in the NMA.

In subgroup NMA, no evidence of clinically meaningful or statistically significant differences were noted by the type of biologic (TNF versus non-TNF biologic; receptor versus antibody TNF biologic), biologic dose (SD versus HD versus LD), RA disease duration or trial duration.

Overall completeness and applicability of evidence

ACR50 and withdrawals due to adverse events were reported by almost all of the studies included in this overview and NMA, and data from several studies were available for many other outcomes. Some important outcomes, including radiographic scores and cancer, were reported either by few RCTs (e.g. radiographic scores) or had a low event rate (e.g. cancer), or both, which limited our ability to draw firm conclusions about them for biologics overall and to compare them between biologics. The evidence report is up to date and current, with this 2015 update. Due to the rarity of trials with direct comparisons, this study provides comparisons of biologics to MTX and indirect comparisons of biologics to each other.

Quality of the evidence

For the 2015 update, the quality of included trials was reasonably good. However poor reporting of the conduct of the included trials was a major issue as all were described as double-blind randomized but less than 50% reported adequate sequence generation, allocation concealment and blinding. Forty-two percent reported adequate sequence generation, 37% of trials were judged to be at low risk for allocation concealment, 42% trials were judged at low risk of performance bias (blinding), 47% at low risk of detection bias (blinding), 53% trials had low risk of attrition bias and 89% trials had low risk of major baseline imbalance. Selective reporting bias could not be assessed since for several trials, we could not find published protocols.

The overall quality of the direct evidence for most outcomes (ACR50, HAQ, remission, serious adverse events) was downgraded to moderate due to inconsistency of effect. Direct evidence was low quality for radiographic outcomes, withdrawals due to adverse events and cancer, due to imprecision or indirectness or serious imprecision. The quality of evidence from the NMA for all outcomes was low to moderate quality due to imprecision and indirectness. We did not detect publication bias. Wide credible intervals were only found in some subgroup analyses.

Potential biases in the overview process

Our review has several limitations. Lack of reporting of many important outcomes from RCTs or few events (radiographic scores, cancer, etc.), or both, limited our ability to analyze and compare these outcomes between biologics and comparators and between biologics (TNF versus non-TNF biologic; by dose etc.).

With the introduction of multiple biologics, whose benefits have yet to be compared to one another, it is unclear whether one or more biologics might be more beneficial or safer, or better tailored to different subgroups of participants suffering from RA. To our knowledge there are only few head-to-head comparisons of benefit and safety of various biologics in people with RA. Gabay 2013; Schiff 2008a; and Weinblatt 2013 are the most well-known trials. We included direct comparator studies in our analyses; however, the majority of the studies compared biologic to MTX and two trials to MTX with methylprednisolone. In the absence of such direct comparisons, NMA results that incorporate indirect comparisons can provide useful information although still need to be interpreted with caution.

Indirect comparisons (incorporated into NMA estimates) have several limitations. RCTs differ in patient population characteristics, most prominently in prior failed therapy, biologic dose, concomitant use of DMARDs, mean RA disease duration, and trial duration. To overcome this limitation, we analyzed in the categories of previous DMARD history (MTX-naive, MTX-experienced, DMARD-experienced and TNF-experienced), biologic dose (SD, HD, LD), and concomitant MTX (yes/no). We observed several novel findings when these analyses were performed, which make results of this NMA and overview comprehensive. We also performed a-priori-specified subgroup analyses by the duration of RA (early, established, late) and duration of the trial (less than six, 6 to 12 and more than 12 months) as a surrogate of biologic exposure. These analyses also provide interesting results in specific subpopulations of people with RA. However, subgroup analyses are subject to low power and type II error, that is, missing significant results, by chance, due to lower number of studies and participants. Therefore, these results must be interpreted with caution.

Additionally, some studies presented data on safety for all doses of the biologic together, not just the recommended dose and in some cases presented data for the entire study duration, including the open-label phase. This limited our ability to get the data for the randomized phase or by dose.

One must be careful in interpreting the odds ratios that may look slightly different from each other numerically, but not statistically. It is important to consider the 95% confidence intervals while interpreting these numbers. Due to a large number of comparisons and challenge interpreting these tables, we summarized all statistically significant odds ratios, to the extent possible, in the main text. This should make it easier for readers to interpret the results.

There is also possibility of type-I error, due to multiple comparisons and up to five differences per 100 comparisons may be due to chance. However, given the limited data for most outcomes, short trial duration and rarity of harms outcomes, our main concern with most of these analyses is type-II error, that is, missing an important difference due to small number of events, not type-I error.

Two abstractors abstracted all data independently for this updated 2015 version and the original 2009 version. This we believe minimizes errors in data abstractions, and biases due to this error. Abstract and titles were also reviewed in duplicate independently, to avoid errors, as part of systematic review.

Agreements and disagreements with other studies or reviews

Our NMA and overview was performed using a comprehensive strategy, accounting for many potential factors that differ between trials and trial arms. Therefore, direct comparison of results to most published NMAs is not possible, particularly those that have not stratified participants by these important characteristics.

In general, many results agree with several similar analyses in the past. However, since our review has several more studies than included in the previous reviews/overviews, some estimates differ, as expected. Additionally, our review includes all available studies for biologics, while most previous reviews have included anti-TNF biologics with few exceptions, and many used RCT data from non-standardized doses.

Thompson 2011 conducted a meta-analysis of TNF biologics versus MTX in people with RA with early disease (not necessarily all MTX-naive) and found that the risk of serious infections and cancer with TNF biologics were similar to MTX with an OR of 1.28 (95% CI 0.82 to 2.00) and 1.08 (95% CI 0.50 to 2.32), respectively. Similarly, we found no difference in rates of serious adverse events with biologics versus comparator (MTX/other DMARDs + placebo in most cases) with moderate quality of evidence, but results for the risk of cancer were inconclusive with low quality of evidence.

In a meta-analysis of RCTs of anti-TNF biologics in people with RA who were MTX-naive (Alonso-Ruiz 2008), the RR of achieving ACR20 and ACR50 for biologic monotherapy versus MTX was RR 1.6 (95% CI 1.4 to 1.7) and RR 1.0 (95% CI 0.9 to 1.1) versus comparator. The pattern of these risk ratios are very similar to those reported in our study, although with better power and more studies, we found that the rates of ACR50 were higher in people receiving biologics compared to MTX/other DMARDs with an OR of 1.85 (95% CrI 1.56 to 2.19) or a RR of 1.36 (95% CrI 1.25 to 1.48).

Several systematic reviews and NMAs could not be compared to our study due to significant differences in patient population, since they focused on MTX/other DMARD-failure population and either did not include RCTs from MTX/other DMARD-naive population, or when included, these constituted a small proportion of all RCTs (Bongartz 2006; Bongartz 2009; Donahue 2008; Gartlehner 2006; Lee 2008; Leombruno 2008; Nam 2010; Nixon 2007; Orme 2012). Desai 2012 studied treatment discontinuation, an outcome different than the outcome we included.

AUTHORS' CONCLUSIONS

Implications for practice

In the presence of very few direct head-to-head comparator trials of biologics in people with RA, practitioners are faced with a dilemma when choosing between biologics, for people who are MTX-naive (where this is possible and desirable). This review summarizes the direct and indirect comparator data for biologics, as monotherapy or in combination with MTX in this patient population. This review and NMA can provide guidance for the individual and the healthcare providers, especially when making a decision about starting biologic in MTX-naive people and choosing which one. Our finding that biologic with MTX use in people with RA who are MTX-naive is associated with statistically significant and clinically meaningful benefits in terms of achievement of ACR50, remission and HAQ scores, implies that biologics in combination with MTX could be a reasonable alternative to MTX for some people with active RA; however potential costs and side effects of biologic must be balanced against this and treatment options individualized for each person. However, they are much more costly and in most countries, the use of a biologic is predicated on having demonstrated a failure to respond to MTX and/or other DMARDs. We also found that in those who were MTX-naive, that there was no evidence that the benefit of biologic monotherapy was better than MTX, an important finding. This result further supports the current practice of using MTX first in people with RA who are MTX-naive.

Implications for research

We believe that more RCTs of direct head-to-head comparisons of biologic agents in people with RA are needed. These RCTs should examine the relative benefit and safety of biologics for various stages of the disease (early, established and late RA), various levels of functional limitation (mild, moderate and severe limitation) and in people with variable exposure to other therapies (traditional DMARD-naive, traditional DMARD-failure, biologic-failure, multiple biologic failure). More long-term observational studies and assessments of biologic registry data are needed to determine the longer-term benefits and harms of different treatment strategies for RA.

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ADDITIONAL TABLES

Table 1. Characteristics of included studies

Study name	Biologic(s)	Biologic dose(s)	Number of study arms	Non-biologic comparator	Concomitant use of MTX	Trial duration	RA duration	Biologic-naive	Total number of participants
Bejarano 2008	Adalimumab	SD	2	MTX + PL	Yes	13 months	Established	Yes	148
Bejarano 2010	Infliximab	SD	2	MTX + PL	Yes	8 years	Established	No	20
Breedveld 2006	Adalimumab (+/- MTX)	SD	3	MTX + PL	Yes	24 months	Established	Yes	799
Detert 2013	Adalimumab	SD	2	MTX + PL	Yes	12 months	Early	Yes	172
Durez 2007	Infliximab	SD	2	MP + MTX	Yes	12 months	Early	No	29
Emery 2008 (COMET)	Etanercept	SD	2	MTX + PL	Yes	12 months	Established	Yes	542
Emery 2009 (GO-BEFORE)	Golilumab (+/- MTX)	SD, HD	4	MTX + PL	Yes	12 months	Established	No	637
Kavanaugh 2013 (OPTIMA)	Adalimumab	SD	2	MTX + PL	Yes	6 months	Established	No	1032
Marcora 2006	Etanercept	SD	2	MTX	No	6 months	Unknown	Yes	26
Nam 2014a	Infliximab	SD	2	MP + MTX	Yes	6 months	Early	Yes	112
Nam 2014b	Etanercept	SD	2	MTX + PL	Yes	12 months	Early	Yes	110
Quinn 2005	Infliximab	SD	2	MTX + PL	Yes	12 months	Early	Yes	20
Rantalaiho 2014	Infliximab	SD	2	MTX + PL	Yes	24 months	Early	Yes	93
Soubrier 2009	Adalimumab	SD	2	MTX + PL	Yes	12 months	Established	No	65
St Clair 2004 (ASPIRE)	Infliximab	SD, HD	3	MTX + PL	Yes	12 months	Early	Yes	1049
Tak 2012	Rituximab	SD, LD	3	MTX + PL	Yes	24 months	Early	Yes	748
Takeuchi 2014	Adalimumab	SD	2	MTX + PL	Yes	6 months	Early	Yes	334

Table 1. Characteristics of included studies *(Continued)*

Tam 2012	Infliximab	SD	2	MTX	Yes	12 months	Established	Yes	40
Westhovens 2009	Abatacept	SD	2	MTX + PL	Yes	24 months	Established	No	509

HD: high dose; LD: low dose; MTX: methotrexate; PL: placebo; SD = standard dose

Table 2. 'Summary of findings' table for biologics vs comparator in MTX/other DMARD-naive people

Comparison			**Direct evidence**			**Network meta-analysis**		
Outcome: ACR50		**No. of participants (studies)**	**RR (95% CI)**	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**	**RR (95% CrI)**	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**
Biologics + MTX	versus comparator	5720 (14 studies)	1.40 (1.30 to 1.49)	16% (13% to 20%) NNTB = 7 (6 to 8)	⊕⊕⊕⊖ moderate (downgraded for inconsistency)[1]	n/a		
TNF biologic alone (without MTX)	versus comparator	850 (2 studies)	0.94 (0.73 to 1.22)	-2% (-11% to 7%) NNTB = n/a	⊕⊕⊕⊖ moderate (downgraded for imprecision)[2]	1.00 (0.82 to 1.21)	0% (-8% to 9%) NNTB = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and indirectness)[2,4]
TNF biologic + MTX	versus comparator	4463 (12 studies)	1.44 (1.34 to 1.54)	17% (13% to 21%) NNTB = 6 (5 to 8)	⊕⊕⊕⊕ high[3]	1.42 (1.30 to 1.54)	18% (13% to 22%) NNTB = 6 (5 to 8)	⊕⊕⊕⊖ moderate (downgraded for indirectness)[4]
Non-TNF biologic + MTX	versus comparator	1257 (2 studies)	1.27 (1.14 to 1.42)	13% (7% to 19%) NNTB = 8 (6 to 14)	⊕⊕⊕⊕ high[3]	1.31 (1.11 to 1.52)	13% (5% to 22%) NNTB = 8 (5 to 22)	⊕⊕⊕⊖ moderate (downgraded for indirectness)[4]

Outcome: HAQ score 0-3 (higher = worse): a measure of function	**No. of participants (studies)**	**Direct evidence**			**Network meta-analysis**		
		MD (95% CI)	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**	**MD (95% CrI)**	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**

Table 2. 'Summary of findings' table for biologics vs comparator in MTX/other DMARD-naive people *(Continued)*

Biologics + MTX	versus comparator	3872 (13 studies)	-0.10 (-0.16 to -0.04)	-3.3% (-5.3% to -1.3%) NNTB = 4 (2 to 15)	⊕⊕⊕⊖ moderate (downgraded for inconsistency)[5]	n/a		
TNF biologic alone (without MTX)	versus comparator	557 (2 studies)	0.09 (-0.24 to 0.41)	3% (-8% to 13.7%) NNTB = n/a	⊕⊕⊕⊖ moderate (downgraded for imprecision)[2]	0.17 (-0.19 to 0.54)	5.7% (-6.3% to 18%) NNTB = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and indirectness)[2,4]
TNF biologic + MTX	versus comparator	2615 (11 studies)	-0.09 (-0.26 to 0.07)	-3% (-8.7% to 2.3%) NNTB = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and inconsistency)[2,6]	-0.08 (-0.25 to 0.07)	-2.7% (-8.3% to 2.3%) NNTB = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and indirectness)[2,4]
Non-TNF biologic + MTX	versus comparator	1257 (2 studies)	-0.22 (-0.26 to -0.18)	-7.3% (-8.7% to -6%) NNTB = 2 (2 to 3)	⊕⊕⊕⊖ moderate (downgraded for inconsistency)[7]	-0.22 (-0.55 to 0.11)	-7.3% (-18.3% to 3.7%) NNTB = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and indirectness)[2,4]
Outcome: Remission (defined as DAS < 1.6 or DAS28 < 2.6)		**No. of participants (studies)**	**Direct evidence**			**Network meta-analysis**		
			RR (95% CI)	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**	**RR (95% CrI)**	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**
Biologics + MTX	versus comparator	5128 (15 studies)	1.62 (1.33 to 1.98)	15% (11% to 19%) NNTB = 5 (6 to 7)	⊕⊕⊕⊖ moderate (downgraded for inconsistency)[8]	n/a		
TNF biologic alone (without MTX)	versus comparator	850 (2 studies)	1.08 (0.83 to 1.41)	2% (-3% to 8%) NNTB = n/a	⊕⊕⊕⊖ moderate (downgraded for imprecision)[2]	1.02 (0.74 to 1.39)	1% (-7% to 11%) NNTB = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and indirectness)[2,4]
TNF biologic + MTX	versus comparator	4463 (12 studies)	1.55 (1.22 to 1.96)	14% (9% to 19%) NNTB = 7 (5 to 10)	⊕⊕⊕⊖ moderate (downgraded for inconsistency)[9]	1.62 (1.40 to 1.86)	18% (12% to 23%) NNTB = 7 (5 to 10)	⊕⊕⊕⊖ moderate (downgraded for indirectness)[4]
Non-TNF biologic + MTX	versus comparator	1257 (2 studies)	2.10 (1.45 to 3.04)	19% (15% to 24%) NNTB = 6 (4 to 9)	⊕⊕⊕⊖ moderate (downgraded for inconsistency)[10]	1.85 (1.46 to 2.28)	24% (13% to 35%)	⊕⊕⊕⊖ moderate (downgraded for indirectness)[4]

Table 2. 'Summary of findings' table for biologics vs comparator in MTX/other DMARD-naive people *(Continued)*

						NNTB = 6 (4 to 10)		
Outcome: Radiographic progression on Sharp/Van der Heijde modification (0-448 points)		**No. of participants (studies)**	**Direct evidence**			**Network meta-analysis**		
			MD (95% CI)	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**	**MD (95% CrI)**	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**
Biologics + MTX	versus comparator	2256 (5 studies)	-2.56 (-6.03 to 0.92)	-0.57% (-1.35% to 0.21%) NNTB = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and inconsistency)[2,11]	n/a		
TNF biologic + MTX	versus comparator	1747 (4 studies)	-3.18 (-6.80 to 0.43)	-0.71% (-1.52% to 959.82%) NNTB = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and inconsistency)[2,12]	-3.73 (-5.78 to -1.62)	-0.83% (-1.29% to -0.36%) NNTB = 3 (3 to 7)	⊕⊕⊕⊖ moderate (downgraded for indirectness)[4]
Non-TNF biologic + MTX	versus comparator	509 (1 study)	-0.43 (-2.04 to 1.18)	-0.22% (-0.46% to 0.26%) NNTB = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and inconsistency)[2,11]	-0.42 (-4.22 to 3.41)	-0.09% (-0.94% to 0.76%) NNTB = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and indirectness)[2,4]
Outcome: Withdrawals due to adverse events		**No. of participants (studies)**	**Direct evidence**			**Network meta-analysis**		
			RR (95% CI)	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**	**RR (95% CrI)**	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**
Biologics + MTX	versus comparator	5800 (14 studies)	1.32 (0.89 to 1.97)	2% (0% to 4%) NNTH = n/a	⊕⊕⊖⊖ low (downgraded for inconsistency and imprecision)[1,2]	n/a		
TNF biologic alone (without MTX)	versus comparator	850 (2 studies)	1.14 (0.62 to 2.10)	0% (-4% to 4%) NNTH = n/a	⊕⊕⊖⊖ low (downgraded for serious imprecision)[13]	0.93 (0.41 to 1.90)	0% (-2% to 3%) NNTH = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and indirectness)[2,4]

Table 2. 'Summary of findings' table for biologics vs comparator in MTX/other DMARD-naive people *(Continued)*

TNF biologic + MTX	versus comparator	4543 (12 studies)	1.60 (1.10 to 2.32)	3% (1% to 4%) NNTH = 35 (17 to 183)	⊕⊕⊕⊖ moderate (downgraded for imprecision)[14]	1.68 (1.16 to 2.56)	3% (1% to 5%) NNTH = 31 (14 to 138)	⊕⊕⊕⊖ moderate (downgraded for indirectness)[4]
Non-TNF biologic + MTX	versus comparator	1257 (2 studies)	0.56 (0.31 to 1.01)	-2% (-5% to 1%) NNTH = n/a	⊕⊕⊖⊖ low (downgraded for serious imprecision)[13]	0.56 (0.25 to 1.29)	-2% (-3% to 1%) NNTH = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and indirectness)[2,4]
Outcome: Serious adverse events		**No. of participants (studies)**	**Direct evidence**			**Network meta-analysis**		
			RR (95% CI)	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**	**RR (95% CrI)**	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**
Biologics + MTX	versus comparator	4850 (12 studies)	1.05 (0.87 to 1.26)	1% (-1% to 3%) NNTH = n/a	⊕⊕⊕⊖ moderate (downgraded for imprecision)[2]	n/a		
TNF biologic alone (without MTX)	versus comparator	319 (1 study)	0.46 (0.16 to 1.29)	-4% (-8% to 1%) NNTH = n/a	⊕⊕⊖⊖ low (downgraded for serious imprecision)[13]	0.52 (0.16 to 1.30)	-5% (-9% to 3%) NNTH = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and indirectness)[2,4]
TNF biologic + MTX	versus comparator	3593 (10 studies)	1.14 (0.92 to 1.42)	1% (-1% to 3%) NNTH = n/a	⊕⊕⊕⊖ moderate (downgraded for imprecision)[2]	1.16 (0.90 to 1.51)	2% (-1% to 4%) NNTH = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and indirectness)[2,4]
Non-TNF biologic + MTX	versus comparator	1257 (2 studies)	0.87 (0.64 to 1.18)	-1% (-5% to 2%) NNTH = n/a	⊕⊕⊖⊖ low (downgraded for serious imprecision)[13]	0.87 (0.57 to 1.34)	-1% (-4% to 3%) NNTH = n/a	⊕⊕⊖⊖ low (downgraded for imprecision and indirectness)[2,4]
Outcome: Cancer (***note: Peto OR used but can interpret as RR due to low event rate***)		**No. of participants (studies)**	**Direct evidence**			**Network meta-analysis**		
			RR (95% CI)	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**	**RR (95% CrI)**	**Absolute risk difference, NNTB**	**Quality of evidence (GRADE)**
Biologics + MTX	versus comparator	4611 (11 studies)	0.71 (0.38 to 1.33)	0% (0% to 0%) NNTH = n/a	⊕⊕⊖⊖ low (downgraded for serious imprecision)[13]	n/a		

Table 2. 'Summary of findings' table for biologics vs comparator in MTX/other DMARD-naive people *(Continued)*

TNF biologic alone (without MTX)	versus comparator	850 (2 studies)	0.79 (0.24 to 2.61)	0% (-2% to 1%) NNTH = n/a	⊕⊕◯◯ low (downgraded for serious imprecision)[13]	0.94 (0.25 to 3.18)	0% (-1% to 2%) NNTH = n/a	⊕⊕◯◯ low (downgraded for imprecision and indirectness)[2,4]
TNF biologic + MTX	versus comparator	3863 (10 studies)	0.77 (0.35 to 1.69)	0% (0% to 0%) NNTH = n/a	⊕⊕◯◯ low (downgraded for serious imprecision)[13]	0.81 (0.36 to 1.73)	0% (-1% to 0%) NNTH = n/a	⊕⊕◯◯ low (downgraded for imprecision and indirectness)[2,4]
Non-TNF biologic + MTX	versus comparator	748 (1 study)	0.62 (0.22 to 1.77)	0% (-3% to 1%) NNTH = n/a	⊕⊕◯◯ low (downgraded for serious imprecision)[13]	0.64 (0.20 to 2.12)	0% (-1% to 1%) NNTH = n/a	⊕⊕◯◯ low (downgraded for imprecision and indirectness)[2,4]

Comparator = MTX and/or DMARD
GRADE Working Group grades of evidence
High quality (⊕⊕⊕⊕) : we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality (⊕⊕⊕◯) : we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality (⊕⊕◯◯) : our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality (⊕◯◯◯) : we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect
CI: confidence interval; CrI; credible interval; DAS: Disease Activity Score; DMARD: disease-modifying anti-rheumatic drug; MTX: methotrexate; n/a: not available; NNTB/NNTH: number needed to treat for an additional beneficial/harmful outcome; OR: odds ratio; RR: risk ratio; TNF: tumor necrosis factor
[1]Downgraded for inconsistency: I^2= 51%.
[2]Downgraded for imprecision: 95% CI estimate includes both null effect and appreciable benefit or harm.
[3]No evidence of imprecision or inconsistency. Number of events > 300.
[4]Downgraded for indirectness/intransitivity due to differing participant characteristics (established vs late RA; types of failures); differing biologic doses and co-interventions; and differing comparators.
[5]Downgraded for inconsistency: I^2= 93%.
[6]Downgraded for inconsistency: I^2= 90%.
[7]Downgraded for inconsistency: I^2= 95%.
[8]Downgraded for inconsistency: I^2= 75%.
[9]Downgraded for inconsistency: I^2= 81%.
[10]Downgraded for inconsistency: I^2= 65%.
[11]Downgraded for inconsistency: I^2= 97%.
[12]Downgraded for inconsistency: I^2= 96%.
[13]Downgraded twice for serious imprecision - few events (< 300) and 95% CI estimate includes both null effect and appreciable benefit or harm.
[14]Downgraded for imprecision - few events (< 300)

APPENDICES

Appendix 1. Characteristics of excluded studies

Study	Reason for exclusion
Abe 2006	Wrong drug exposure
Axelsen 2015	Duplicate of Hørslev-Petersen 2014
Bae 2013	Wrong drug exposure
Bathon 2000	Duplicate of Genovese 2002
Bonafede 2015	Not a RCT
Bingham 2015	Wrong drug exposure
Burmester 2013	Comparing two routes of administration of a biologic
Burmester 2015	Wrong drug exposure
Chen 2009	Wrong drug exposure
Cheng 2014	Conference abstract
Choy 2012	Wrong drug exposure
Cohen 2002	Wrong drug exposure
Cohen 2003	Wrong drug exposure
Cohen 2004	Wrong drug exposure
Cohen 2006	Wrong drug exposure
Combe 2006	Wrong drug exposure
Conaghan 2013	Wrong drug exposure
Conaghan 2014	Sub-study of Huizinga 2015
Dougados 2014	Duplicate of Huizinga 2015
Doyle 2013	Wrong drug exposure
Durez 2004	Wrong drug exposure
Emery 2006	Wrong drug exposure
Emery 2010	Wrong drug exposure
Emery 2014a	Duplicate
Emery 2014b	Conference abstract

(Continued)

Ericksson 2015	Follow-up at two years of Van Vollenhoven 2012a NCT00764725
Fleischmann 2003	Wrong drug exposure
Fleischmann 2009	Wrong drug exposure
Fleischmann 2013	Conference abstract
Furst 2003	Wrong drug exposure
Furst 2007	Wrong drug exposure
Furst 2015	Open label study
Gabay 2013	Wrong drug exposure
Gashi 2014	Comparing two doses of a biologic
Genovese 2004	Wrong drug exposure
Genovese 2005	Wrong drug exposure
Genovese 2008	Wrong drug exposure
Genovese 2011	Wrong drug exposure
Genovese 2014	Wrong drug exposure
Gherge 2014	Conference abstract
Goekoop-Ruiterman 2007	Wrong drug exposure
Haraoui 2014	Duplicate of Pope 2014
Heimans 2014	Wrong drug exposure
Hobbs 2015	Wrong drug exposure
Hørslev-Petersen 2014	Open label study
Iannone 2014	Open label study
Johnsen 2006	Wrong drug exposure
Jones 2010	Wrong drug exposure
Kaine 2012	Wrong drug exposure
Kameda 2011	Wrong drug exposure
Kavanaugh 2014	Conference abstract
Kay 2008	Wrong drug exposure
Kennedy 2014	Wrong drug exposure

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Keystone 2004a	Wrong drug exposure
Keystone 2004b	Wrong drug exposure
Keystone 2008	Wrong drug exposure
Keystone 2014	Conference abstract
Kim 2007	Wrong drug exposure
Kim 2012	Wrong drug exposure
Kim 2013	Wrong drug exposure
Kivitz 2014	Vaccine response study
Koroleva 2014a	Conference abstract
Koroleva 2014b	Conference abstract
Kremer 2003	Wrong drug exposure
Kremer 2005	Wrong drug exposure
Kremer 2006	Wrong drug exposure
Kremer 2011	Wrong drug exposure
Kremer 2009	Wrong drug exposure
Kremer 2015	Cross over study design
Lan 2004	Wrong drug exposure
Landewe 2015	Conference abstract
Lipsky 2000	Wrong drug exposure
Lisbona 2008	Wrong drug exposure
Lisbona 2010	Wrong drug exposure
Machado 2014	Wrong drug exposure
Maini 1999	Wrong drug exposure
Manders 2015	Trial participants switched therapy within one year/before completion of study period
Mathias 2000	Wrong drug exposure
McInnes 2015	Compares lipid levels in those randomized to CZP or PL, in MTX-IR patients
Moreland 2002	Wrong drug exposure
Navarro 2014	Conference abstract

(Continued)

Nishimoto 2009	Wrong drug exposure
O'Dell 2013	Wrong drug exposure
Oakley 2014	Conference abstract
Pavelka 2013	Sub-group analysis of Smolen 2013 NCT00565409
Rau 2004	Wrong drug exposure
Rigby 2011	Duplicate of Tak 2011
Rubbert-Roth 2010	Wrong drug exposure
Schiff 2004	Wrong drug exposure
Schiff 2008a	Wrong drug exposure
Schiff 2014	Wrong drug exposure
Smolen 2008	Wrong drug exposure
Smolen 2009	Wrong drug exposure
Smolen 2013	Wrong drug exposure
Smolen 2014	Participants in the control group also received the intervention
Smolen 2015	Wrong drug exposure
Sonomoto 2014	Open label study
Strand 2012	Wrong drug exposure
Tak 2011	Wrong drug exposure
Tanaka 2011	Wrong drug exposure
Tanaka 2012	Wrong drug exposure
Taylor 2004	Wrong drug exposure
Taylor 2006	Wrong drug exposure
Van der Heidje 2013	Wrong drug exposure
Van der Kooij 2009	Wrong drug exposure
Van Vollenhoven 2009	Wrong drug exposure
Van Vollenhoven 2012a	Duplicate of Van Vollenhoven 2009
Van Vollenhoven 2012b	Wrong drug exposure
Vital 2015	B cell depletion study

(Continued)

Weinblatt 1999	Wrong drug exposure
Weinblatt 2003	Wrong drug exposure
Weinblatt 2006	Wrong drug exposure
Weinblatt 2007	Wrong drug exposure
Weinblatt 2008	Wrong drug exposure
Weinblatt 2012	Wrong drug exposure
Weinblatt 2013a	Wrong drug exposure
Weinblatt 2013b	Wrong drug exposure
Weinblatt 2014	Results at 1 year of Weinblatt 2013b GO-FURTHER trial, NCT00973479
Weisman 2003	Wrong drug exposure
Weisman 2007	Wrong drug exposure
Westhovens 2006	Wrong drug exposure
Westhovens 2014	Conference abstract
Yamamoto 2014a	Wrong drug exposure
Yamanaka 2014	Post hoc analysis of Takeuchi 2014
Yazici 2012	Wrong drug exposure
Zhang 2006	Wrong drug exposure

CZP: certolizumab pegol; MTX-IR: methotrexate inadequate responder; PL: placebo; RCT: randomised controlled trial

Appendix 2. Ongoing trials from the WHO trial register and Clinicaltrials.gov

NCT Number	Title
ACTRN12605000784617	A phase IIIb multi-center, randomized, double-blind study to evaluate remission and joint damage progression in methotrexate naive early erosive RA subjects treated with abatacept plus methotrexate compared with methotrexate
ACTRN12605000785606	A phase II study of abatacept versus placebo to assess the prevention of rheumatoid arthritis (RA) in adult patients with undifferentiated arthritis who are at high risk for the development of RA
ACTRN12606000248561	A phase 1 randomised double blind, placebo-controlled, single dose, dose escalation study of kb002, a chimeric monoclonal antibody which binds to granulocyte macrophage-colony stimulating factor (gm-csf), in patients with rheumatoid arthritis

(Continued)

ACTRN12608000397314	Multi-national open-label study to evaluate the safety, tolerability and efficacy of tocilizumab versus tocilizumab plus non-biologic disease modifying antirheumatic drugs in patients with active rheumatoid arthritis
ACTRN12609000747224	Extension phase of the multi-national open-label study to evaluate the safety, tolerability and efficacy of tocilizumab in patients with active rheumatoid arthritis on background non-biologic disease-modifying anti-rheumatic drugs (DMARDs) who have an inadequate response to current non-biologic DMARD and/or anti tumor necrosis factor (anti-TNF) therapy
ACTRN12610000284066	A longitudinal study of patients with rheumatoid arthritis starting biological therapy; assessment of joint inflammation by use of ultrasonography
ACTRN12611000972921	The hunter Humira and endothelial function in early rheumatoid arthritis trial
ACTRN12611001202954	A comparison of arthroscopic synovial biopsy based targeted biologic therapy versus conventional therapy in rheumatoid arthritis (RA)
ACTRN12614000903684	A randomized, single-blind, single-dose, 3-arm, parallel group study to determine the pharmacokinetic similarity of abp 710 and infliximab (Remicade 'registered trademark') in healthy adult subjects
ACTRN12615000557538	Hunter heart-RA-2 (HHRA-2) study: a randomised controlled trial evaluating the effects of Humira upon cardiovascular risk as measured by endothelial function in patients with rheumatoid arthritis who test positive for anti-CCP antibodies as well as those who test negative for anti-CCP antibodies
ChiCTR-CCC-10001054	Circulating dickkopf-1 (DKK-1) is correlated with bone erosion and inflammation in rheumatoid arthritis
ChiCTR-IIR-16008693	Pharmacokinetics, safety and tolerability study of single dose of abatacept 125mg administered subcutaneously
ChiCTR-INR-16009546	The efficacy and safety of low dose il-2 combined il-6 antagonist therapy in Chinese over-treated patients with rheumatoid arthritis
ChiCTR-TRC-09000383	Efficacy and safety of recombinant human il-1 receptor antagonist in Chinese patients with rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial
ChiCTR-TRC-10001060	Efficacy and safety of infliximab in Chinese patients with rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial
CTRI/2008/091/000295	A clinical trial to study the safety and effectiveness of a monoclonal antibody in combination with methotrexate in patients with active rheumatoid arthritis
CTRI/2012/05/002660	A clinical study to demonstrate safety and efficacy data to support the development of R-TPR-015 (1422015) in patients with active rheumatoid arthritis on stable dose of methotrexate
CTRI/2013/05/003678	A randomized controlled study to evaluate pharmacokinetic, pharmacodynamic (efficacy) and safety of rituximab (Zydus) and rituximab (Roche) in patients with rheumatoid arthritis
CTRI/2013/09/003963	Study to compare the safety and efficacy of etanercept of Intas biopharmaceuticals ltd against Enbrel® in patients with active rheumatoid arthritis
CTRI/2013/10/004040	A study to evaluate efficacy, tolerability and safety of adalimumab (Zydus) and adalimumab (Reference) in patients with rheumatoid arthritis
CTRI/2014/04/004571	A clinical trial to study the effects of two drugs, R-TPR-021 / Humira® in patients with active rheumatoid arthritis on a stable dose of methotrexate

(Continued)

CTRI/2014/07/004742	Phase III clinical trial comparing efficacy and safety of BCD-020 (CJSC BIOCAD, Russia) and Mabthera® (f. Hoffmann-la Roche ltd, Switzerland) in patients with rheumatoid arthritis.
CTRI/2014/09/004954	A clinical trial to study the effects of three anti-cd20 monoclonal antibodies in patients with moderate to severe active, seropositive rheumatoid arthritis with an inadequate response to methotrexate based therapy
CTRI/2015/01/005398	A study to determine pharmacodynamics (effect of drug in the body) and to compare pharmacokinetics (how drug behaves in the body), safety and tolerability of single dose of Lupin's Rituximab with Roche's Rituximab following I.V. infusion in patients with rheumatoid arthritis
CTRI/2016/02/006625	A clinical trial to evaluate efficacy and safety of BMO-2 and adalimumab in patients with active rheumatoid arthritis
CTRI/2016/04/006884	A clinical study to evaluate the efficacy, safety, immunogenicity, and pharmacokinetics of subcutaneous injection of adalimumab (test product, Hetero) and reference medicinal product (reference product, Abbvie) concomitantly administered with methotrexate in patients with rheumatoid arthritis
CTRI/2016/05/006899	A study to compare the biosimilar of etanercept (coded as YLB113) made by YLBiologics with Enbrel (originator's etanercept) in patients suffering from rheumatoid arthritis with respect to its efficacy, safety and antibody formation
CTRI/2016/07/007097	Multi-centre, randomized, double-blind, two-arm, parallel group, comparative clinical study to evaluate pharmacokinetic, efficacy and safety of etanercept in patients with active rheumatoid arthritis
DRKS00011083	Clinical study of an anthroposophic treatment strategy for early rheumatoid arthritis, compared to conventional long-term therapy
EUCTR2004-000563-96-HU	A 24-month, randomized, double-blind, two period study to evaluate the efficacy and safety of the combination of etanercept and methotrexate and methotrexate alone in subjects with active early rheumatoid arthritis: combination of methotrexate and etanercept
EUCTR2004-000922-59-SE	A phase III, multi-center, randomized, double-blind, placebo-controlled comparative study of abatacept or infliximab in combination with methotrexate in controlling disease activity in subjects with rheumatoid arthritis having an inadequate clinical response to methotrexate
EUCTR2004-002620-18-DE	A multi-national randomized, double-blind, exploratory study of abatacept versus placebo in preventing the development of rheumatoid arthritis in adult subjects with undifferentiated inflammatory arthritis at high risk for the development of rheumatoid arthritis
EUCTR2004-002993-49-HU	A phase III multicentre, double blind, placebo-controlled, parallel group 52-week study to assess the efficacy and safety of 2 dose regimens of lyophilised cdp870 given subcutaneously as additional medication to methotrexate in the treatment of signs and symptoms and preventing structural damage in patients with active rheumatoid arthritis who have an incomplete response to methotrexate
EUCTR2004-003295-10-GB	A multicenter, randomized, double-blind, placebo-controlled trial of golimumab, a fully human anti-TNFalfa monoclonal antibody, administered subcutaneously, in methotrexate-naïve subjects with active rheumatoid arthritis
EUCTR2004-003296-36-DE	A multicenter, randomized, double-blind, placebo-controlled trial of golimumab, a fully human anti-TNFalfa monoclonal antibody, administered subcutaneously, in subjects with active rheumatoid arthritis despite methotrexate therapy

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EUCTR2004-003299-12-FI	A multicenter, randomized, double-blind, placebo-controlled trial of golimumab, a fully human anti-TNFalfa monoclonal antibody, administered subcutaneously, in subjects with active ankylosing spondylitis
EUCTR2004-003733-14-FI	A study investigating whether tocilizumab (study drug) prevents joint damage, and how safe it is, in patients with moderate to severe rheumatoid arthritis randomly divided to groups receiving treatment with tocilizumab and methotrexate or methotrexate and placebo
EUCTR2004-003741-40-AT	A randomized, double-blind, parallel group study of the safety and reduction of signs and symptoms during treatment with MRA versus placebo, in combination with methotrexate, in patients with moderate to severe active rheumatoid arthritis
EUCTR2004-003771-37-HU	A double-blind, randomized, placebo controlled, dose escalation, multi-center phase I/II trial of humax-cd20, a fully human monoclonal anti-cd20 antibody, in patients with active rheumatoid arthritis who have previously failed one or more disease modifying anti-rheumatic drugs. - humax-cd20 in active rheumatoid arthritis, phase I/II
EUCTR2004-005210-37-DE	A randomized, double-blind, placebo-controlled, parallel group study of the safety and reduction of signs and symptoms during treatment with MRA versus placebo, in combination with traditional DMARD therapy in patients with moderate to severe active rheumatoid arthritis and an inadequate response to current DMARD therapy
EUCTR2005-000492-18-IT	Insulin resistance and endothelial dysfunction TNF-alpha dependent in patients with rheumatoid arthritis or metabolic syndrome
EUCTR2005-000674-43-GB	An open label study of the effect of treatment with rituximab on resistant rheumatoid arthritis: clinical, radiological, synovial and immunological outcomes - rituximab in rheumatoid arthritis
EUCTR2005-000784-26-GB	A phase IIIb multi-center, randomized, double-blind study to evaluate remission and joint damage progression in methotrexate naive early erosive RA subjects treated with abatacept plus methotrexate compared with methotrexate revised protocol 04
EUCTR2005-000884-25-DE	A randomized, double-blind, placebo-controlled, parallel group study of the safety and reduction of signs and symptoms during treatment with MRA versus placebo, in combination with methotrexate in patients with moderate to severe active rheumatoid arthritis and an inadequate response to previous anti-TNF therapy.
EUCTR2005-001138-33-LT	A randomized, double-blind, double-dummy, parallel group study of the safety and efficacy of MRA monotherapy, versus methotrexate (MTX) monotherapy, in patients with active rheumatoid arthritis.
EUCTR2005-001549-41-HU	A randomised, double-blind study comparing the safety and efficacy of etanercept with sulphasalazine in subjects with ankylosing spondylitis - ASCEND
EUCTR2005-001633-14-DK	Randomised, multi-center, open-label, parallel-group study comparing adalimumab (Humira) 40 mg s.c. EOW versus infliximab (Remicade®) 3 mg/kg i.v. every 6. week in RA patients with unsustainable clinical response to infliximab 3 mg/kg every 8. week - The SWITCH Study
EUCTR2005-001742-16-GB	A multicenter, randomized, double-blind, placebo-controlled trial of golimumab, a fully human anti-TNFalfa monoclonal antibody, administered subcutaneously in subjects with active rheumatoid arthritis and previously treated with biologic anti-TNFalfa agent(s) - go-after
EUCTR2005-001889-13-SE	Randomised controlled trial evaluating strategies to optimize disease activity control in RA patients treated with infliximab in clinical practice
EUCTR2005-002326-63-LT	A phase III multi–center, double–blind, placebo–controlled, parallel group 24–week study to assess the efficacy and safety of two dose regimens of liquid certolizumab pegol as additional medication to methotrexate

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EUCTR2005-002392-32-IE	A randomised, placebo controlled, double-blind, parallel group, international study to evaluate the safety and efficacy of rituximab (Mabthera/Rituxan) in combination with methotrexate, compared to methotrexate monotherapy, in patients with active rheumatoid arthritis
EUCTR2005-002395-15-FI	A randomized, phase 3, controlled, double-blind, parallel-group, multicenter study to evaluate the safety and efficacy of rituximab in combination with methotrexate (MTX) compared to MTX alone, in methotrexate-naïve patients with active rheumatoid arthritis
EUCTR2005-002396-33-ES	A randomised, double-blind, international study to evaluate the efficacy and safety of various re-treatment regimens of rituximab in combination with methotrexate in RA patients with an inadequate response to methotrexate
EUCTR2005-002423-13-DE	Long-term extension study of safety during treatment with tocilizumab (MRA) in patients completing treatment in WA17822
EUCTR2005-002909-23-ES	Long-term extension study of safety during treatment with tocilizumab (MRA) in patients completing treatment in MRA core studies
EUCTR2005-003632-22-ES	A study of the pharmacokinetic and pharmacodynamic activity of rituximab in combination with methotrexate (MTX) in synovial tissue and in peripheral blood of patients with rheumatoid arthritis
EUCTR2005-004530-40-AT	Induction of remission in RA patients at low disease activity by additional infliximab-therapy
EUCTR2005-004582-41-GB	Safety and efficacy of combination treatment with rituximab and leflunomide in patients with active rheumatoid arthritis - rituximab and leflunomide in RA
EUCTR2005-005013-37-GB	A multi-centre randomised double dummy double blind study comparing two regimens of combination induction therapy in early DMARD naive rheumatoid arthritis: the IDEA study (infliximab as induction therapy in early rheumatoid arthritis) - IDEA
EUCTR2005-005358-27-GB	Efficacy of rituximab (Mabthera) in active ankylosing spondylitis: a clinical and magnetic resonance imaging study
EUCTR2006-000363-28-GB	Differentiating the mechanism of action of anti TNF-alpha agents - data study
EUCTR2006-000854-32-AT	Rituximab in rheumatoid arthritis in patients who failed therapy with TNF-blockers
EUCTR2006-001000-37-DE	Efficacy and safety of rituximab in patients with rheumatoid arthritis - FIRST
EUCTR2006-001428-38-GB	Remission induction in very early rheumatoid arthritis (RIVERA): a comparison of etanercept plus methotrexate plus steroid with standard therapy - RIVERA
EUCTR2006-001553-10-BE	A 26-week, phase II, multi-center, randomized, double-blind, placebo-controlled study to assess the response to treatment (ACR50) and to determine a biomarker profile in responders to ACZ885 (anti-interleukin-1beta monoclonal antibody) plus MTX as compared to MTX alone in early rheumatoid arthritis patients
EUCTR2006-003843-22-IT	Prospective study on intensive early rheumatoid arthritis treatment with adalimumab: induction of remission and maintenance - 'CURE' A phase IV multicenter, randomized, double-blind study
EUCTR2006-004139-31-BE	A multicenter, randomized, double-period, double-blind study to determine the optimal protocol for treatment initiation with methotrexate and adalimumab combination therapy in patients with early rheumatoid arthritis - OPTIMA
EUCTR2006-004673-98-HU	Efficacy of rituximab treatment in patients with rheumatoid arthritis having inadequate response to TNF blocker

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EUCTR2006-005137-38-FR	A 3 month, randomised, open label, parallel group, descriptive study to explore and compare perceptions and satisfaction for two different delivery mechanisms for etanercept (etanercept autoinjector and the etanercept prefilled syringe)
EUCTR2006-005157-29-FR	Effet du methotrexate sur la relation dose - effet de l'infliximab dans la spondylarthrite ankylosante - SPAXIM
EUCTR2006-005386-19-BE	Cytokines and inflammatory proteins gene expression study in synovial biopsies from rheumatoid arthritis patients refractory to anti-TNF therapy treated with rituximab - anti TNF resistant RA / RTX / mini
EUCTR2006-005640-81-GB	A placebo controlled study of the effect of extended treatment with rituximab on resistant rheumatoid arthritis: - EXXTRA
EUCTR2006-006127-40-GB	Cerebral blood flow following TNF-alpha antagonism in rheumatoid arthritis - a pilot study - TNF/cbf in RA
EUCTR2006-006186-16-NL	Improved: induction therapy with methotrexate and prednisone in rheumatoid or very early arthritic disease a randomized clinical trial in patients with recent-onset arthritis to compare the efficacy of DMARD combination therapy including prednisone with combination therapy including adalimumab, a TNF-blocking agent - IMPROVED
EUCTR2006-006275-21-GB	A randomised, pragmatic, open-label study of adalimumab versus etanercept for rheumatoid arthritis. - adalimumab versus etanercept for RA
EUCTR2006-006591-37-BE	A 3 month, randomised, open label, parallel group, descriptive study to explore and compare perceptions and satisfaction for two different delivery mechanisms for etanercept (etanercept auto-injector and the etanercept prefilled syringe)
EUCTR2006-006746-33-DE	Re-treatment with rituximab in patients with rheumatoid arthritis who have had an inadequate response to not more than one a TNF (extension study to ML19070) - efficacy of re-therapy in anti-TNFalpha IR
EUCTR2007-000082-38-DK	The OPERA Study. Optimized treatment algorithm in early rheumatoid arthritis: Methotrexate and intra-articular glucocorticosteroid plus adalimumab or placebo in the treatment of early rheumatoid arthritis. A Randomised, double-blind and placebo-controlled, two arms, parallel group study of the additive effect of adalimumab concerning inflammatory control and inhibition of erosive development. - The OPERA Study
EUCTR2007-000593-24-GB	An open-label, observational study of the effects of anti-TNF therapy on peripheral blood and synovial biomarkers in patients with active rheumatoid arthritis
EUCTR2007-000828-40-FR	A phase IIIb, multi-centre, double-blind randomized, placebo-controlled, parallel group 52-week study to evaluate safety and efficacy of the PEGylated anti-TNFα Fab′fragment, certolizumab pegol, administered concomitantly with stable-dose DMARDs in patients with moderate to low disease activity rheumatoid arthritis
EUCTR2007-000896-41-HU	A randomized, double-blind study comparing the safety and efficacy of once-weekly administration of etanercept 50 mg, etanercept 25 mg, and placebo in combination with methotrexate in subjects with moderately active rheumatoid arthritis
EUCTR2007-001190-28-GB	Randomised controlled trial of tumour-necrosis-factor inhibitors against combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis - TACIT
EUCTR2007-001420-12-BE	A randomised, double-blind (with open comparator etanercept limb), placebo-controlled, phase IIb, multicentre study to evaluate the efficacy of 4 doses of azd9056 administered for 6 months on the signs and symptoms of rheumatoid arthritis

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EUCTR2007-001585-33-LT	A randomized, placebo controlled, multicenter clinical study investigating efficacy of rituximab (Mabthera®/Rituxan®) in the inhibition of joint structural damage assessed by magnetic resonance imaging in patients with rheumatoid arthritis and inadequate response to methotrexate - the R.A. Score study
EUCTR2007-001625-10-HU	An open-label, randomized study to evaluate the radiographic efficacy and safety of Enbrel™ (etanercept) added to methotrexate in comparison with usual treatment in subjects with moderate rheumatoid arthritis disease activity - EXTRA
EUCTR2007-001754-11-IT	Pilot study to evaluate the effect of rituximab in combination with MTX in the inhibition of progression of synovitis, bone marrow edema, and erosions evaluated by magnetic resonance imaging (MRI) in the hand of patients with rheumatoid arthritis
EUCTR2007-002066-35-HU	A phase 2B, randomized, double-blind, placebo controlled active comparator, multicenter study to compare 5 dose regimens of CP-690,550 and adalimumab versus placebo, administered for 6 months in the treatment of subjects with active rheumatoid arthritis
EUCTR2007-002536-29-FR	A randomised, double-blind, placebo controlled, multi-centre phase II study of atacicept in anti-TNF alfa-naïve patients with moderate to severely active rheumatoid arthritis and an inadequate response to methotrexate - atacicept in anti-TNF alfa-naïve subjects with RA
EUCTR2007-003096-39-IT	Effects of etanercept on endothelial function and carotid intima-media thickness in patients with active ankylosing spondylitis: a 52-weeks, randomized, double blind, placebo-controlled study - crest
EUCTR2007-003288-36-NL	A phase 4, multicenter, open-label, assessor-blinded, switch study of the efficacy and safety of infliximab (Remicade) in patients with active rheumatoid arthritis who are responding inadequately to etanercept (Enbrel) of adalimumab (Humira)
EUCTR2007-003358-27-DE	Phase III, multi-center, randomized, double blind, placebo-controlled study for treatment of juvenile ankylosing spondylitis with adalimumab - Humira Study
EUCTR2007-003623-20-ES	Estudio de los efectos de la terapia anti-célula b (rituximab) sobre la inmunopatología del tejido sinovial y las células b de sangre periférica en artritis reumatoide (estudio tesice-ar). Study of the b-cell-targeted therapy (rituximab) effects on the synovial tissue inmunopathology and peripheral blood b cells in rheumatoid arthritis (tesice-ar study)
EUCTR2007-003647-75-NL	A randomised, double-blind, placebo controlled, multi-centre, exploratory, pilot, phase II trial of 150 mg atacicept given subcutaneously in combination with rituximab in subjects with rheumatoid arthritis. - atacicept in combination with rituximab in subjects with rheumatoid arthritis
EUCTR2007-004694-26-BE	A comparative study of a 6-month infliximab (Remicade) or placebo regimen in undifferentiated arthritis at high risk for the development of rheumatoid arthritis: clinical, radiological (MRI) and synovial benefit
EUCTR2007-005464-26-GB	Development of heart and blood vessel problems in patients with conditions which cause long-term, widespread, inflammation in the body
EUCTR2007-005905-23-DE	A multi-center, randomized, double-blind, placebo-controlled study comparing 80 mg of adalimumab with placebo, and demonstrating the non-inferiority of monthly 80 mg adalimumab dosing compared with 40 mg adalimumab every other week dosing
EUCTR2007-006657-63-FI	Study comparing the effect on disease activity when reducing or discontinuing etanercept in subjects with rheumatoid arthritis (RA)
EUCTR2007-007539-14-CZ	A randomised, double-blind, placebo-controlled, phase IIb dose-ranging study (with open-label etanercept treatment group) to investigate efficacy, safety and pharmacokinetics of azd5672 administered for 12 weeks to rheumatoid arthritis patients receiving methotrexate

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EUCTR2008-000105-11-DE	Effectiveness after 4 and 24 weeks and safety of tocilizumab in patients with active RA - TAMARA - tocilizumab and DMARDs: achievements in rheumatoid arthritis
EUCTR2008-000587-17-GB	Multi-national open-label study to evaluate the safety, tolerability and efficacy of tocilizumab in patients with active rheumatoid arthritis on background non-biologic DMARDs who have an inadequate response to current non-biologic DMARD and/or anti-TNF therapy
EUCTR2008-001241-26-HU	A randomized, placebo-controlled, double-blind, dose escalation study to evaluate the efficacy, safety and tolerability of the study drug bt971 in patients with rheumatoid arthritis receiving concomitant methotrexate
EUCTR2008-002381-55-ES	Evaluación de la eficacia de rituximab en pacientes con artritis reumatoide a través de la medición, por resonancia magnética de mano, de los parámetros clínicos de la enfermedad. Estudio resonar. Efficacy of rituximab in patients with rheumatoid arthritis, by measurement of disease parameters through magnetic resonance of the hand. RESONAR study
EUCTR2008-002623-85-NL	A 3-phase study to evaluate sustained remission and productivity outcomes in subjects with early rheumatoid arthritis initiated on treatment with etanercept plus methotrexate
EUCTR2008-002631-33-GB	Randomized, placebo controlled, double blind, multi-center phase II proof-of-concept study to assess the efficacy of ain457 in patients with moderate to severe ankylosing spondylitis
EUCTR2008-003011-12-GB	Prospective randomised double-blind placebo controlled study assessing the efficacy of tocilizumab with synovial analysis in patients with rheumatoid arthritis - TOCRA
EUCTR2008-004126-16-FI	Local open-label study to evaluate the safety and efficacy of tocilizumab in patients with active rheumatoid arthritis on background non-biologic DMARDs who have an inadequate response to current non-biologic DMARDs
EUCTR2008-004931-39-PL	A study to determine the safety, efficacy, and pharmacokinetics of 80 mg, 160 mg, and 320 mg ald518 versus placebo administered as multiple intravenous infusions to patients with active rheumatoid arthritis who have had an inadequate response to methotrexate
EUCTR2008-005212-40-SE	Pain mechanisms and fatigue in rheumatoid arthritis (RA) and healthy volunteers. Can antirheumatic and biological therapy affect pain processing and fatigue in RA?
EUCTR2008-005320-81-AT	A 2-year open-label second extension study to evaluate the safety, tolerability and efficacy of canakinumab (acz885) an anti-interleukin-1ß monoclonal antibody in patients with active rheumatoid arthritis
EUCTR2008-005450-20-BE	The cost-effectiveness of abatacept, rituximab or anti-TNF alpha for patients with rheumatoid arthritis. - Dutch Rheumatoid Arthritis Monitoring (DREAM) Targetted Immune Modulator Evaluation (TIME)
EUCTR2008-005525-11-ES	Estudio randomizado, controlado con placebo, doble ciego y con grupos paralelos para comparar la seguridad y la reducción de la actividad de la enfermedad con la combinación de rituximab (Mabthera) y tocilizumab (roactemra) frente al tratamiento con tocilizumab en pacientes con artritis reumatoide activa con respuesta incompleta a metotrexato. A randomized, placebo controlled, double-blind, parallel group study to compare the safety and efficacy of the combination of rituximab (Mabthera) and tocilizumab (Actemra) versus tocilizumab therapy in patients with active rheumatoid arthritis with an incomplete response to methotrexate
EUCTR2008-006256-22-FR	Evaluation by high resolution micro computerized tomography of bone microarchitecture changes in patients with rheumatoid arthritis under anti-TNF therapy
EUCTR2008-006885-27-NL	Efficacy and safety of adalimumab (Humira®) in patients with peripheral spondyloarthritis without ankylosing spondylitis or psoriatic arthritis

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EUCTR2008-006924-68-AT	Extension phase of the multi-national open-label study to evaluate the safety, tolerability and efficacy of tocilizumab in patients with active rheumatoid arthritis on background non-biologic DMARDs who have an inadequate response to current non-biologic DMARD and/or anti-TNF therapy.
EUCTR2008-006936-37-HU	A randomized, parallel, double-blind, placebo-controlled study to evaluate the efficacy and safety of ILV-094 administered subcutaneously to subjects with active rheumatoid arthritis on a stable background of methotrexate
EUCTR2008-008338-35-CZ	Phase 3 randomized, double-blind, active comparator, placebo-controlled study of the efficacy and safety of 2 doses of CP 690,550 in patients with active rheumatoid arthritis on background methotrexate
EUCTR2009-010582-23-DE	A golimumab phase 3b, multicenter, switch assessment of subcutaneous and intravenous efficacy in rheumatoid arthritis patients who have inadequate disease control despite treatment with etanercept (Enbrel®) or adalimumab (Humira®)
EUCTR2009-010955-29-NL	Prevention of clinically manifest rheumatoid arthritis by B cell directed therapy in the earliest phase of the disease
EUCTR2009-011105-17-IT	A single-arm, open-label study of early improvement of anemia and fatigue during treatment with tocilizumab (TCZ) in combination with non biologic DMARDs, in adult patients with moderate to severe active rheumatoid arthritis
EUCTR2009-011137-26-DE	An open-label study assessing the addition of subcutaneous golimumab (GLM) to conventional disease-modifying antirheumatic drug (DMARD) therapy in biologic-naïve subjects with rheumatoid arthritis (part 1), followed by a randomized study assessing the value of combined intravenous and subcutaneous GLM administration aimed at inducing and maintaining remission (part 2)
EUCTR2009-011520-53-SK	Evaluation of adherence and persistence to tocilizumab in combination with methotrexate or tocilizumab monotherapy in patients with moderate to severe active rheumatoid arthritis in local environment
EUCTR2009-011591-30-GB	An open-label non-randomized extension study to evaluate the safety and tolerability of ain457 (anti interleukin-17 monoclonal antibody) in patients with moderate to severe ankylosing spondylitis
EUCTR2009-011719-19-FR	Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of certolizumab pegol in subjects with active axial spondyloarthritis
EUCTR2009-012185-32-IT	Open label, multicentric phase IIIb study to evaluate the effect of tocilizumab in combination with DMARDs in the inhibition of progression of synovitis, bone marrow edema, and erosions evaluated by dedicated magnetic resonance imaging (MRI) in the hand of patients with rheumatoid arthritis (RA)
EUCTR2009-012204-42-IE	A randomized, double-blind, placebo-controlled, parallel group study to investigate the ability of gsk706769 to maintain clinical efficacy after withdrawal of Enbrel in patients with rheumatoid arthritis
EUCTR2009-012218-30-PT	A randomized, double-blind, placebo-controlled study to assess the efficacy of tocilizumab (TCZ) + non-biological DMARD in reducing synovitis as measured by magnetic resonance imaging (MRI) at 12 weeks after initiation of treatment in patients with moderate to severe rheumatoid arthritis (RA) with inadequate response to non-biological DMARDs
EUCTR2009-012759-12-GB	A multi-center, randomized, double-blind, parallel group study of the safety, disease remission and prevention of structural joint damage during treatment with tocilizumab (TCZ), as a monotherapy and in combination with methotrexate (MTX), versus methotrexate in patients with early, moderate to severe rheumatoid arthritis

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EUCTR2009-013316-12-NL	A multi-center, randomized, double blind, placebo controlled study to evaluate remission in DMARD and biological naïve early rheumatoid arthritis (RA) subjects treated with tocilizumab (TCZ) plus tight control methotrexate (MTX) treatment, TCZ monotherapy or tight control MTX monotherapy. - U-ACT-EARLY
EUCTR2009-013758-33-SE	Multicenter study with a 16-week double-blind, placebo-controlled (during the initial 2 weeks) randomized period, followed by a 24-week open label extension to assess magnetic resonance image-verified early response to certolizumab pegol in subjects with active rheumatoid arthritis
EUCTR2009-015515-40-NL	Prevention of the progression of very early symptoms into ankylosing spondylitis: a placebo controlled trial with etanercept
EUCTR2009-015653-20-NL	Prospective study on the effects of etanercept treatment in patients with rheumatoid arthritis who are naïve for TNF-alpha blocking therapy and patients who do not respond (anymore) to prior treatment with other anti-TNF-alpha medication
EUCTR2009-015740-42-DE	A phase 3, multicenter, randomized, open, prospective, controlled, parallel-group study of reduction of therapy in patients with rheumatoid arthritis in ongoing remission RETRO
EUCTR2009-015845-21-GB	A multi-center, randomized, blinded, parallel-group study of the reduction of signs and symptoms during monotherapy treatment with tocilizumab 8 mg/kg intravenously versus adalimumab 40 mg subcutaneously in patients with rheumatoid arthritis
EUCTR2009-015950-39-DE	Rituximab-treatment in addition to leflunomide in patients with active rheumatoid arthritis
EUCTR2009-016789-10-NL	Efficacy of the H1N1 flu (swine flu) vaccination in patients with rheumatoid arthritis treated with rituximab
EUCTR2009-017325-19-FI	The effect of six months adalimumab treatment on sick leaves and retirement in patients with rheumatoid arthritis who are at risk of losing their ability to work
EUCTR2009-017443-34-GB	A ph II/III seamless, multi-center, randomized, double-blind, placebo-controlled study of the reduction in signs and symptoms and inhibition of structural damage during treatment with tocilizumab versus placebo in patients with ankylosing spondylitis who have failed non-steroidal anti-inflammatory drugs and are naïve to TNF antagonist therapy
EUCTR2009-017488-40-GB	A randomized, double-blind, parallel-group placebo-controlled study of the safety and reduction of signs and symptoms during treatment with tocilizumab (TCZ) versus placebo in patients with ankylosing spondylitis who have had an inadequate response to previous TNF antagonist therapy
EUCTR2010-018331-18-GB	A 52 week, single center, open-label study to evaluate neutrophil function and survival effects of tocilizumab (TCZ) in patients with active rheumatoid arthritis (RA) on background non-biologic DMARDs who have an inadequate response to current non-biologic DMARD and/or anti-TNF therapy
EUCTR2010-018375-22-ES	A randomized, double-blind, parallel group study of the safety and effect on clinical outcome of tocilizumab sc versus tocilizumab iv, in combination with traditional disease modifying anti-rheumatoid arthritis drugs (DMARDs), in patients with moderate to severe active rheumatoid arthritis. Estudio randomizado, doble ciego, con grupos de tratamiento paralelos, para evaluar la seguridad y el efecto sobre el resultado clínico de tocilizumab sc frente a tocilizumab iv en combinación con fármacos antirreumáticos modificadores de la enfermedad (FAMEs) tradicionales, en pacientes con artritis reumatoide activa moderada a severa
EUCTR2010-019694-15-BE	Act-alone: an open-label, single-arm study to describe glucocorticoid use in rheumatoid arthritis patients treated with tocilizumab in daily clinical practice and to evaluate systematic glucocorticoid dose reduction once low disease activity is reached

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EUCTR2010-019873-13-BE	Comparative study of the clinical response and cardiorespiratory endurance in early rheumatoid arthritis patients treated with tociluzimab or methotrexate addendum protocol: global gene expression profiles in synovial biopsies from early rheumatoid arthritis patients treated with tocilizumab or methotrexate -TOMERA
EUCTR2010-019935-37-FI	A pragmatic, randomized, parallel group study of the effect on disease remission, work productivity, and tolerability of tocilizumab in combination with DMARDs and individually designed best practice DMARD therapy in patients with early, moderate to severe rheumatoid arthritis
EUCTR2010-020738-24-GB	To see whether for patients with established rheumatoid arthritis that have already achieved a good response to tumour necrosis factor inhibitor (TNF inhibitor) treatment, whether the treatment be tapered to a minimum dose without affecting the control of disease activity
EUCTR2010-020839-39-GB	Efficacy and safety of cdp6038 in patients with rheumatoid arthritis with an unsuccessful response to anti-TNF therapy
EUCTR2010-020913-10-GB	An open label, pilot, multi-centre, step-down, randomised controlled trial to examine whether etanercept 25mg once weekly is effective in maintaining a clinical response in patients with ankylosing spondylitis who have responded to 50mg once weekly
EUCTR2010-021020-94-DE	A randomized, double-blind, parallel-group, placebo- and active calibrator-controlled study assessing the clinical benefit of sar153191 subcutaneous (sc) on top of methotrexate (MTX) in patients with active rheumatoid arthritis (RA) who have failed previous TNF-a anatagonists
EUCTR2010-022049-88-DE	"Efficacy and safety study of a sequential therapy of tocilizumab (TCZ) and, if initially inadequately responded to tocilizumab (TCZ), followed by rituximab (RTX) in DMARD-ir patients with rheumatoid arthritis (MIRAI)" - MIRAI
EUCTR2010-022378-15-DE	A clinical study to explore the therapeutic effects of different doses of the new drug veltuzumab, a drug of biologic origin, and placebo, in patients with rheumatoid arthritis
EUCTR2010-023910-30-GB	A prospective, single-centre, randomised study evaluating the clinical, imaging and immunological depth of remission achieved by very early versus delayed etanercept in patients with rheumatoid arthritis (VEDERA)
EUCTR2010-023956-99-HU	Phase IIB rheumatoid arthritis dose ranging study for BMS-945429 in subjects who are not responding to methotrexate
EUCTR2011-000215-79-FR	Tociluzimab effect on endothelial function in patients with rheumatoid arthritis - TEFRA
EUCTR2011-001626-15-ES	A study of Roactemra/Actemra (tocilizumab) in combination with methotrexate in patients with rheumatoid arthritis with inadequate response to prior treatment with methotrexate and low disease activity with the combination de Roactemra/Actemra y methotrexate
EUCTR2011-001729-25-DE	Study designed to demonstrate the efficacy and safety of certolizumab pegol in combination with methotrexate in the treatment of subjects suffering from early, progressive active rheumatoid arthritis
EUCTR2011-001863-39-AT	A study of safety and efficacy of tocilizumab (TCZ) in combination with methotrexate (MTX) versus tocilizumab monotherapy in patients with mild to moderate rheumatoid arthritis, who have not adequately responded to their current treatment with MTX
EUCTR2011-002275-41-CZ	A study of two different adalimumab formulations in adults with rheumatoid arthritis
EUCTR2011-002325-22-GB	Study of ixekizumab in participants with active ankylosing spondylitis (AS)
EUCTR2011-002363-15-IS	A clinical trial with the aim to explore infusion reactions from tocilizumab given either in 31 or 60 minutes to patients with moderate to severe rheumatoid arthritis

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EUCTR2011-004017-17-GB	Tocilizumab and remission in early rheumatoid arthritis
EUCTR2011-004171-36-CZ	A study comparing sait101 to Mabthera® in subjects with severe rheumatoid arthritis (RA)
EUCTR2011-004468-31-GB	Evaluating the long-term safety and efficacy effects of ct-p13 together with methotrexate in patients with arthritis
EUCTR2011-005021-48-HU	A study to investigate and compare the efficacy, safety, tolerability and pharmacodynamic (biochemical and physiological effects of the drug) of tl011 and Mabthera® (rituximab) in patients with severe, active rheumatoid arthritis treated with methotrexate (MTX)
EUCTR2011-005204-15-AT	Could ultrasound help to identify the patients with rheumatoid arthritis, in those the treatment with biological DMARDs could be stopped?
EUCTR2011-005260-20-GB	Roactemra® (tocilizumab) plus methotrexate (MTX) in stable dosage in comparison with Roactemra® plus reducing (tapering) MTX dosages in patients with severe rheumatoid arthritis (RA) that have inadequate responded to a trial of two disease modifying anti-rheumatic drugs (DMARDs), including MTX and have not been previously treated with a biologic agent, such as a TNF inhibitor
EUCTR2011-005448-87-HU	A study of the maintenance of efficacy of etanercept plus DMARD(s) compared with DMARD(s) alone in subjects with rheumatoid arthritis after achieving an adequate response with etanercept plus DMARD(s)
EUCTR2011-005649-10-DE	An exploratory clinical study to investigate mavrilimumab, an antibody being developed for the treatment of moderate to severe rheumatoid arthritis, an inflammatory condition that affects the joints versus a different antibody whose mechanism works by inhibiting tumor necrosis factor
EUCTR2011-006001-10-IT	Efficacy of rituximab at the dose of 500 mg e.v., two infusions two weeks apart, versus rituximab at the usual dose of 1000 mg, two infusions two weeks apart, in patients affected by rheumatoid arthritis, who had been previously treated with rituximab at the standard dose for at least two cycles obtaining a good clinical response
EUCTR2011-006040-79-DK	The efficacy and safety of adding tocilizumab to methotrexate and intra-articular glucocorticosteroid treatment in early rheumatoid arthritis.
EUCTR2011-006125-14-HU	A multicenter, open-label, single arm, long term extension study of WA19926 to describe safety during treatment with tocilizumab in patients with early, moderate to severe rheumatoid arthritis - function LTE
EUCTR2012-000139-21-AT	Multi-center biomarker trial to predict therapeutic responses of patients with rheumatoid arthritis to a specific biologic mode of action
EUCTR2012-001760-30-IT	Evaluation effects of treatment with an inhibitor of the receptor of a protein (interleukin-6 il-6)involved in inflammatory process, on the clinical response and on the changes from baseline in the biomarkers in patients with rheumatoid arthritis (RA)not responding adequately to disease-modifying antirheumatic drugs (DMARDs) and/or to a first biological agent
EUCTR2012-002009-23-HU	Clinical trial to demonstrate that treatments with gp2015 and Enbrel® are comparable in patients with rheumatoid arthritis
EUCTR2012-002322-73-HU	A phase 3 study in moderate to severe rheumatoid arthritis
EUCTR2012-002535-28-GB	A randomised, open labelled study in anti-TNFa inadequate responders to investigate the mechanisms for response - resistance to rituximab versus tocilizumab in RA (r4-ra)
EUCTR2012-003057-29-CZ	A multi-centre, randomised, double-blind multiple dose study of increasing doses of xmab5871 in patients with rheumatoid arthritis

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EUCTR2012-003194-25-LT	Bioequivalence trial of Mabioncd20® (Mabion SA) compared to reference product: Mabthera® (rituximab, Roche) in patients with rheumatoid arthritis
EUCTR2012-003536-23-CZ	To evaluate the safety of sar153191 (REGN88) and tocilizumab added to other RA drugs in patients with RA who are not responding to or intolerant of anti-TNF therapy (Saril-RA-Ascertain)
EUCTR2012-003644-71-ES	Randomized, double-blind, placebo-controlled trial of etanercept plus methotrexate in monoclonal antibody (MAB) anti-TNF failure
EUCTR2012-003876-38-DE	Clinical study to find out if the biologically similar medicine gp2013 is safe in patients with rheumatoid arthritis who have been treated with Rituxan® or Mabthera® in the past
EUCTR2012-004482-40-ES	Evaluation of a protocol for the reduction of doses in patients with rheumatoid arthritis (RA) in clinical remission in treatment with biological therapies
EUCTR2012-005026-30-HU	A study comparing SB4 to Enbrel® in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy
EUCTR2012-005275-14-NO	Remission in rheumatoid arthritis – assessing withdrawal of disease-modifying antirheumatic drugs
EUCTR2012-005733-37-CZ	A study comparing SB2 to Remicade® in subjects with moderate to severe rheumatoid arthritis
EUCTR2013-000337-13-DE	Prediction of response to certolizumab pegol treatment with MRI of the brain. A multi-center, randomized double-blind controlled study prediction of response to certolizumab-pegol in rheumatoid arthritis (PRECEPRA)
EUCTR2013-000342-19-NL	A clinical trial where patients with rheumatoid arthritis are treated with the study drug tocilizumab, subcutaneous (injection in the skin), with or without other non-biological anti-rheumatic drugs, to study the safety and efficacy of the drug
EUCTR2013-000525-31-GB	A randomized, double-blind, phase 3 Study of ABP 501 efficacy and safety compared to adalimumab in subjects with moderate to severe rheumatoid arthritis
EUCTR2013-001569-17-IT	A national, open-label, single-arm, phase IIIb study to evaluate the efficacy of weekly tocilizumab subcutaneous, administered as monotherapy or in combination with other non-biological medicinal products in rheumatoid arthritis (RA) patients
EUCTR2013-002007-34-FI	Safety and efficacy study of tocilizumab injected under the skin in patients with active rheumatoid arthritis (RA) and inadequate response to disease modifying antirheumatic drugs
EUCTR2013-002150-79-BE	A study to evaluate the efficacy and safety of tocilizumab subcutaneous in RA patients
EUCTR2013-002429-52-ES	Study to evaluate the efficacy, safety and tolerability of subcutaneous (SC) tocilizumab (TCZ) in subjects with rheumatoid arthritis
EUCTR2013-002777-22-GB	Targeted Ultrasound in Rheumatoid Arthritis (TURA)
EUCTR2013-003177-99-SE	A clinical study to evaluate the safety of two different doses of tofacitinib for the treatment of rheumatoid arthritis
EUCTR2013-003413-18-GB	Arthritis prevention with abatacept
EUCTR2013-004051-20-ES	Not controlled study to assess the efficacy of tocilizumab in patients with moderate or severe rheumatoid arthritis who are candidates to be treated with a biological therapy as monotherapy

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EUCTR2013-004148-49-LT	Randomized study of pf-06438179 and infliximab in combination with methotrexate in subjects with moderately to severely active rheumatoid arthritis
EUCTR2013-004555-21-AT	A randomized, controlled, double-blind, parallel-group, phase 3 study to compare the pharmacokinetics, efficacy and safety between ct-p10, Rituxan and Mabthera in patients with rheumatoid arthritis
EUCTR2013-005543-90-HU	A randomized, double-blind study to compare pharmacokinetics and pharmacodynamics, efficacy and safety of ABP 798 with rituximab in subjects with moderate to severe rheumatoid arthritis
EUCTR2014-000109-11-DE	Study to assess the efficacy and safety of FKB327 compared with Humira®, when each is administered in combination with methotrexate in patients with rheumatoid arthritis
EUCTR2014-000110-61-CZ	Study to assess the long-term efficacy and safety of FKB327 compared with Humira®, when each is administered in combination with methotrexate in patients with rheumatoid arthritis
EUCTR2014-002374-36-SE	A study with dose de-escalation of conventional or biologic treatments in early rheumatoid arthritis in patients with low disease activity
EUCTR2014-002945-23-GB	A 24-week randomized, open-label, parallel-group, active-controlled, exploratory, proof-of-mechanism imaging study investigating the efficacy of 150 mg of namilumab administered subcutaneously vs adalimumab in patients with moderate to severe early rheumatoid arthritis inadequately responding to methotrexate - a phase 2 study of namilumab vs anti-tumor necrosis factor in patients with rheumatoid arthritis
EUCTR2014-003255-54-CZ	A study evaluating the effects of rgb-03 and Mabthera combined with methotrexate in patients with rheumatoid arthritis
EUCTR2014-003307-30-HU	Multiple dose study of ucb4940 as add-on to certolizumab pegol in subjects with rheumatoid arthritis
EUCTR2014-003453-34-EE	Study of a new drug's effect in people with rheumatoid arthritis who have not responded sufficiently well to treatment with methotrexate
EUCTR2014-003529-16-GB	Stratification of biologic therapies for rheumatoid arthritis by pathobiology
EUCTR2014-004558-33-Outside-EU/EEA	A multicenter, open-label study of the safety, efficacy, and pharmacokinetics of the human anti-TNF monoclonal antibody adalimumab in children with polyarticular juvenile rheumatoid arthritis
EUCTR2014-004673-16-DE	Randomized, blinded, controlled study to compare the efficacy of treatment with tocilizumab with or without glucocorticoids in rheumatoid arthritis
EUCTR2014-004704-29-ES	This trial is designed to determine what effects the human body has on the investigational medicine, ABP 710, and what effects the body has on the investigational medicine after you have been given it, and if this is comparable to what is seen for the licensed medicine, infliximab, in patients with moderate or severe rheumatoid arthritis (RA). This study will assess if the investigational medicine is safe and effective in treating moderate or severe RA compared to the licensed medicine
EUCTR2014-004868-38-GR	A study comparing the use of etanercept and methotrexate, used either alone or in combination, for maintaining remission in rheumatoid arthritis
EUCTR2014-004904-31-NL	A clinical study to investigate the infliximab serum concentration of Remsima™ (infliximab biosimilar) after switching from Remicade (infliximab) in subjects with Crohn's disease (CD), ulcerative colitis (UC) or rheumatoid arthritis (RA) in stable remission
EUCTR2014-005368-13-HU	A study comparing sait101 to Mabthera® or Rituxan® in patients with rheumatoid arthritis (RA)

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EUCTR2015-000581-58-CZ	A randomized,biomarker trial to predict therapeutic responses of patients with rheumatoid arthritis to a specific biologic mode of action
EUCTR2015-001246-28-BE	Ultrasound scores as imaging biomarkers of early response to subcutaneous tocilizumab in association with methotrexate in early rheumatoid arthritis (TOVERA study)
EUCTR2015-001894-41-HU	Multicenter study to evaluate efficacy and safety of certolizumab pegol in subjects with active inflammation in the spine with no damage on x-rays
EUCTR2015-002284-42-FI	INTENT: immunogenicity in patients failing response on anti-TNF
EUCTR2015-002466-22-Outside-EU/EEA	A randomized, multi-center, blinded, placebo-controlled study with an open label run-in period to evaluate the efficacy, safety, and pharmacokinetics of daily, single, subcutaneous injections of r-methuil-1ra (anakinra) in polyarticular-course juvenile rheumatoid arthritis
EUCTR2015-002809-12-HU	A study to compare ylb113 and Enbrel for the treatment of rheumatoid arthritis
EUCTR2015-003433-10-CZ	ADMYRA Trial: clinical trial to compare treatment with GP2017 and Humira® in patients with rheumatoid arthritis
EUCTR2015-004386-91-PL	Study to explore and compare the effects of a new drug in combination with methotrexate therapy in people with early and established rheumatoid arthritis.
EUCTR2015-004858-17-NL	Remission induction in very early rheumatoid arthritis
EUCTR2015-005307-83-CZ	Study of the efficacy and safety of Olokizumab in patients with moderately to severely active rheumatoid arthritis inadequately controlled by methotrexate therapy
EUCTR2016-000933-37-HU	Study to compare abt-494 to abatacept in subjects with rheumatoid arthritis on stable dose of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) who have an inadequate response or intolerance to biologic DMARDs (select-choice)
EUCTR2016-002125-11-LV	Evaluating efficacy, pharmacokinetics and safety between subcutaneous CT-P13 and intravenous CT-P13 in patients with active rheumatoid arthritis
EUCTR2016-002852-26-HU	MSB11022 in moderately to severely active rheumatoid arthritis
EUCTR2016-002908-15-NL	Redo study: research into the effects of lower doses rituximab in patients with rheumatoid arthritis
IRCT201206266302N3	Comparative analysis of Altebrel® (aryogen) with Enbrel®
IRCT2014090319025N1	Efficacy of Mabasia (adalimumab) in rheumatoid arthritis
IRCT2015030321315N1	The effect of adalimumab on treatment of rheumatoid arthritis
ISRCTN14909030	Rituximab in rheumatoid arthritis: is a reduced dose every 6 months equally effective as the regular dose if the patient has low or very low disease activity?
ISRCTN15819795	Effect of anakinra (soluble interleukin-1 receptor antagonist) as combination therapy: second UK combination therapy in early rheumatoid arthritis
ISRCTN23348591	A placebo controlled study of the effect of extended treatment with rituximab on resistant rheumatoid arthritis: clinical and radiological outcomes
ISRCTN27093749	Rituximab in rheumatoid arthritis in patients who failed therapy with tumour necrosis factor-blockers: a multi-centre clinical observational real-life study (phase IIIb)

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ISRCTN29665463	A placebo-controlled trial of anti-TNFa chimeric monoclonal antibody (infliximab, Remicade) in the modification of vascular disease markers in active rheumatoid arthritis
ISRCTN36745608	A controlled randomised double-blind multicentre study comparing two therapy strategies in disease modifying anti-rheumatic drug-naive early rheumatoid arthritis patients over 48 weeks: induction therapy with adalimumab and methotrexate over 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate monotherapy
ISRCTN39045408	Anti-tumour necrosis factor (anti-TNF) therapy over two years increases body fat mass in early rheumatoid arthritis
ISRCTN44880063	Differentiating the mechanism of action of anti-TNF alpha agents
ISRCTN46017566	Arthritis prevention in the pre-clinical phase of rheumatoid arthritis with abatacept
ISRCTN48638981	A multicentre randomised double-blind placebo-controlled study comparing two regimens of combination induction therapy in early disease-modifying anti-rheumatic drug naïve rheumatoid arthritis
ISRCTN49682259	Remission induction in very early rheumatoid arthritis: a comparison of etanercept plus methotrexate plus steroid with standard therapy
ISRCTN51200229	Randomised double blind trial of safety of anti-tumour necrosis factor (anti-TNF) chimeric monoclonal antibody (infliximab) in combination with methotrexate compared to methotrexate alone in patients with rheumatoid arthritis on standard disease modifying anti-rheumatic drugs
ISRCTN57761809	Effect of anti-tumour necrosis factor alpha (TNFa) therapy on blood vessel health in patients with rheumatoid arthritis
ISRCTN62900439	Leflunomide or methotrexate plus subcutaneous tumour necrosis factor-alpha (TNF-alpha) blocking agents in rheumatoid arthritis
ISRCTN70800019	Effects on tocilizumab drug therapy on fat tissue proteins in rheumatoid arthritis
ISRCTN75505683	Remission induction study in early rheumatoid arthritis (RA)
ISRCTN82317088	Changes in bone density and bone turnover in patients with rheumatoid arthritis treated with rituximab, a b cell depleting antibody
ISRCTN89222125	Switching to alternative tumour-necrosis factor (TNF)-blocking drugs or abatacept or rituximab in patients with rheumatoid arthritis who have failed an initial TNF-blocking drug
ISRCTN95861172	Randomised efficacy and discontinuation study of etanercept and adalimumab (RED SEA): a pragmatic open label study in rheumatoid arthritis
ISRCTN97686858	A randomized, controlled study of intra-articular injections of etanercept or glucocorticosteroids in patients with rheumatoid arthritis
JPRN-JapicCTI-111620	A randomized, double-blind, phase I/II study of CT-P13 compared with Remicade in patients with rheumatoid arthritis
JPRN-JapicCTI-142505	Phase III study of MRA-SC 162 mg/week
JPRN-JapicCTI-142621	Chs-0214 phase III trial
JPRN-UMIN000000512	Efficacy of tacrolimus in rheumatoid arthritis patients who have been treated unsuccessfully with infliximab and methotrexate

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JPRN-UMIN000001240	The efficacy of tocilizumab to patients with rheumatoid arthritis refractory to anti-TNF agents: the open trial
JPRN-UMIN000001407	The efficacy and safety of the new biologic agents (humanized anti-human interlukin-6 receptor monoclonal antibody) on abnormal lipid metabolism and atherosclerosis for rheumatoid arthritis patients in Japan
JPRN-UMIN000001798	Prevention of cartilage destruction in rheumatoid arthritis by etanercept (PRECEPT study)
JPRN-UMIN000002110	Discontinuation of infliximab therapy after acquisition of low disease activity by infliximab in rheumatoid arthritis study: RRR (remission induction by Remicade) study
JPRN-UMIN000002246	Study for predictors of effectiveness in tocilizumab therapy (PETITE)
JPRN-UMIN000002340	Comparison of effects between higher dosages of infliximab and switching to other biologics for rheumatoid arthritis patients with less responsiveness to infliximab therapy (Chamlet)
JPRN-UMIN000002421	Multicenter, open-label parallel-groups study comparing tocilizumab versus conventional treatment in rheumatoid arthritis with the complication of AA amyloidosis
JPRN-UMIN000002687	Enbrel clinical outcome in RA patients for growing evidence
JPRN-UMIN000002744	Success of tocilizumab in RA patients with remission induction and sustained efficacy after discontinuation
JPRN-UMIN000003344	Induction of the remission by use of infliximab in RA
JPRN-UMIN000003880	Keeping cartilaginous quality by adalimumab in patient with rheumatoid arthritis in Kansai area
JPRN-UMIN000004412	Corticosteroid-sparing effect of Actemra in patients with rheumatoid arthritis refractory to anti-TNF agents, methotrexate and corticosteroid
JPRN-UMIN000005113	Evaluation of the clinical remission and its sustainment after discontinuation of infliximab in patients with rheumatoid arthritis who receive "programmed" treatment in randomized controlled trial
JPRN-UMIN000005590	Maintenance of remission by tocilizumab mono-therapy after remission obtained by combination with methotrexate in patients with rheumatoid arthritis
JPRN-UMIN000006914	Postmarketing surveillance for investigating success in achieving clinical and functional remission and sustaining efficacy with tocilizumab in biologics naive RA patients
JPRN-UMIN000006956	Efficacy and safety of tocilizumab in RA patients in daily clinical practice: an retrospective observational study
JPRN-UMIN000007019	Efficacy and safety of tocilizumab mono-therapy in patients with adult-onset Still's disease
JPRN-UMIN000007086	An observational study for investigating success in achieving clinical, structural and functional remission and sustaining efficacy with tocilizumab
JPRN-UMIN000007380	Comparison of the effects of single high-dose methotrexate and methotrexate-tocilizumab therapy on rheumatoid arthritis
JPRN-UMIN000007432	Prospective research of infliximab treatment in active RA patients refractory to anti-interleukin six receptor monoclonal antibody

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JPRN-UMIN000007786	Effect examination of infliximab to the effect insufficient example and the example of effect decrease of the 1st TNF inhibitor in rheumatoid arthritis
JPRN-UMIN000007806	The feasibility study of accelated infliximab infusion during maintenance phase
JPRN-UMIN000008185	Pilot study on the efficacy and safety of LD tocilizumab therapy in elderly RA patients
JPRN-UMIN000008281	Dose-escalation study of infliximab or methotrexate based on the disease activity in patients with rheumatoid arthritis treated with infliximab
JPRN-UMIN000008404	Extension of tocilizumab dose intervals in patients with low to moderate disease activity rheumatoid arthritis using il-6 serum level as starting criteria
JPRN-UMIN000008572	The Kitasato Institute non-inferiority trial of etanercept and tacrolimus, the combined therapy with methotrexate in rheumatoid arthritis patients
JPRN-UMIN000008756	Abatacept-based approach to cure of RA
JPRN-UMIN000008812	Efficacy and safety of tocilizumab mono-therapy in patients with large vessel vasculitis (LVV; giant cell arteritis or Takayasu arteritis) and polymyalgia rheumatica (PMR)
JPRN-UMIN000008889	Cohort study of infectious disease risk management in rheumatoid arthritis patients receiving tocilizumab
JPRN-UMIN000009425	A validity inspection study of the treat-to-target strategy with golimumab for the treatment of rheumatoid arthritis patient
JPRN-UMIN000009435	Analysis of factors for bio-free remission due to the tight control by Remicade in rheumatoid arthritis patients. Birdie study
JPRN-UMIN000009887	Associations between the initial concentration of serum TNF alpha and effects due to increasing a dose of infliximab, and between effects of infliximab and the concentration of serum il-6
JPRN-UMIN000010033	To investigate the efficacy of tocilizumab in RA patients with moderate disease activity under biologic therapy
JPRN-UMIN000011520	Keep persistent efficacy by abstaining from biological treatment after numerical SDAI remission with adalimumab (KANSAI study)
JPRN-UMIN000011584	A longitudinal, prospective, multicenter observational study in patients with rheumatoid arthritis receiving tocilizumab
JPRN-UMIN000012005	Identification of bio-markers predicting the therapeutic effects of tocilizumab in rheumatoid arthritis
JPRN-UMIN000012073	Effects of subcutaneous actemra and MTX blending in RA
JPRN-UMIN000012306	Observational study for investigating the ability of recuperation of work/ house work state with tocilizumab (Actemra) subcutaneous treatment in biologics-naive RA patients
JPRN-UMIN000012690	Study of actemra remission induction of RA and sequential maintenance of remission by reasonable cost treatment
JPRN-UMIN000013750	Study on effects of cytokine targeted therapy on periodontal condition in patients with rheumatoid arthritis

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JPRN-UMIN000014311	Examination of the clinical remission and functional remission in infliximab using the increase-in-quantity protocol to TNF-alpha inhibitory drug resistance rheumatoid arthritis
JPRN-UMIN000014484	Saitama Actemra study for QoL in patients with rheumatoid arthritis
JPRN-UMIN000014670	The effect of tocilizumab on synovitis of rheumatoid arthritis. Analysis by musculoskeletal ultrasonography
JPRN-UMIN000014934	A study for effectiveness and safety of tocilizumab therapy in rheumatoid arthritis patients with renal insufficiency
JPRN-UMIN000015175	Head-to-head comparison of subcutaneous tocilizumab versus abatacept for rheumatoid arthritis: prospective, randomized trial
JPRN-UMIN000015297	The feasibility study of accelerated infliximab infusion from initial administration
JPRN-UMIN000015482	Maintenance of remission with 6-week interval of tocilizumab in RA patients who have been in remission
JPRN-UMIN000015616	Biologic mater clinical performance test for ADA and TCZ efficacy prediction
JPRN-UMIN000016844	The clinical study for seeking strategy how to treat rheumatoid arthritis by TNF inhibitors
JPRN-UMIN000016950	Clinical outcome in patients with rheumatoid arthritis switched to tumor necrosis factor blockers after tocilizumab or abatacept
JPRN-UMIN000017230	Correlation between efficacy of the biological therapy (tocilizumab) and levels of oxidative stress markers in Japanese patients with rheumatoid arthritis (inadequate responders to existing therapies)
JPRN-UMIN000017495	Establish the suitable strategy of maintenance therapy for rheumatoid arthritis patient with methotrexate and adalimumab
JPRN-UMIN000017577	Tapering and withdrawal of methotrexate(MTX) or tocilizumab(TCZ), after achievement of RA remission in concomitant use of MTX and TCZ,a randomized control study.
JPRN-UMIN000017947	Efficacy and change of serum il-6 levels in patients with rheumatoid arthritis treated with tocilizumab
JPRN-UMIN000018659	Inhibitory effects of tocilizumab on serum oxidative stress in patients with rheumatoid arthritis -comparison with other biologic agents-
JPRN-UMIN000020799	Efficacy of infliximab as a second bio in patients with refractory rheumatoid arthritis
JPRN-UMIN000020833	The efficacy of iguratimod, and adding adalimumab in patients with active rheumatoid arthritis: an open label multicenter randomized parallel study
JPRN-UMIN000021004	Effectiveness and safety of tocilizumab therapy for rheumatoid arthritis patients
JPRN-UMIN000021048	Longitudinal study about the impact of treatment with tumor necrosis factor (TNF) inhibitors on tuberculin skin test (TST) reaction in patients with rheumatoid arthritis (RA)
JPRN-UMIN000021247	Tocilizumab treatment with reducing and stopping methotrexate in patients with rheumatoid arthritis in stable low disease activity-state
JPRN-UMIN000021492	To investigate the safety of switch from infliximab biosimilar 1 in rheumatoid arthritis patients

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JPRN-UMIN000021929	Optimization of infliximab withdrawal strategy for rheumatoid arthritis
JPRN-UMIN000023006	Usefullness of infliximab as a second tumor necrosis factor inhibitor in patients with rheumatoid arthritis with inadequate response to tumor necrosis factor inhibitor
JPRN-UMIN000024025	The clinical impact of methotrexate dose reduction at combination therapy with adalimumab plus methotrexate in rheumatoid arthritis; ALIBABA study
JPRN-UMIN000024071	Serious infections after tocilizumab administration in patients with rheumatoid arthritis: a retrospective study using an adverse drug reaction database -analysis of clinical symptoms and laboratory test data in serious infections
KCT0000089	Identification of the best treatment strategy in Korean patients with early rheumatoid arthritis
NCT00000433	Blocking tumor necrosis factor in ankylosing spondylitis
NCT00001862	TNRF:Fc to treat eye inflammation in juvenile rheumatoid arthritis
NCT00001901	Etanercept to treat Wegener's granulomatosis
NCT00001954	Etanercept therapy for Sjögren's syndrome
NCT00006070	Etanercept (Enbrel) to treat pain and swelling after third molar extraction
NCT00006292	Infliximab for the treatment of early rheumatoid arthritis
NCT00012506	The safety and efficacy of a tumor necrosis factor receptor fusion protein on uveitis associated with juvenile rheumatoid arthritis
NCT00029042	Infliximab to treat children with juvenile rheumatoid arthritis
NCT00034060	The role of cytokines on growth hormone suppression in premenopausal women with rheumatoid arthritis and the effect of treatment with etanercept
NCT00036374	A study of the safety and effectiveness of infliximab (Remicade) in patients with juvenile rheumatoid arthritis
NCT00036387	A study of the safety and effectiveness of infliximab (Remicade) in patients with rheumatoid arthritis.
NCT00037648	Juvenile rheumatoid arthritis
NCT00037700	Evaluation of the efficacy of combination treatment with anakinra and pegsunercept in improving rheumatoid arthritis
NCT00048568	A phase III study of abatacept (BMS-188667) in patients with active rheumatoid arthritis and inadequate response to methotrexate
NCT00048581	Phase III study of BMS-188667 (CTLA4IG) in patients with rheumatoid arthritis who are currently failing anti-TNF therapy or who have failed anti-TNF therapy in the past
NCT00048932	A phase III study of bms-188667 in subjects with active rheumatoid arthritis
NCT00069329	Anakinra to treat patients with neonatal onset multisystem inflammatory disease
NCT00074438	Study to assess the efficacy and safety of rituximab in patients with rheumatoid arthritis

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NCT00075075	Infliximab to treat non-infectious scleritis
NCT00078806	Safety and efficacy study of etanercept (Enbrel®) in children with systemic onset juvenile rheumatoid arthritis
NCT00094341	Preference of rheumatoid arthritis (RA) patients of Enbrel® (etanercept) auto-injector versus Enbrel® pre-filled syringes
NCT00094900	Interleukin-1 trap to treat autoinflammatory diseases
NCT00095147	Abatacept and infliximab in combination with methotrexate in subjects with rheumatoid arthritis
NCT00095173	BMS-188667 in children and adolescents with juvenile rheumatoid arthritis
NCT00101829	Anti-CD20 antibody therapy for Sjögren's syndrome
NCT00106522	A study to assess the effect of tocilizumab + methotrexate on signs and symptoms in patients with moderate to severe active rheumatoid arthritis currently on methotrexate therapy
NCT00106535	A study to assess the effect of tocilizumab + methotrexate on prevention of structural joint damage in patients with moderate to severe active rheumatoid arthritis (RA)
NCT00106548	A study to assess the effect of tocilizumab + methotrexate on signs and symptoms in patients with moderate to severe active rheumatoid arthritis
NCT00106574	A study to assess the effect of tocilizumab + DMARD therapy on signs and symptoms in patients with moderate to severe active rheumatoid arthritis
NCT00109408	A study to assess the safety and efficacy of tocilizumab in patients with active rheumatoid arthritis
NCT00111410	Evaluating the effect of anakinra (r-methuil-1ra) on vaccine antibody response in subjects with rheumatoid arthritis (RA)
NCT00115219	Evaluating efficacy and safety of etanercept 50 mg twice weekly (biw) in rheumatoid arthritis (RA) subjects who are sub-optimal responders to etanercept 50 mg once weekly (qw)
NCT00121043	Evaluating Kineret® (anakinra) in rheumatoid arthritis (RA) subjects using a self-reported questionnaire
NCT00122382	Remission and joint damage progression in early rheumatoid arthritis
NCT00124449	Study of abatacept versus placebo to assess the prevention of rheumatoid arthritis (RA) in adult patients
NCT00132418	Study of Enbrel in rheumatoid arthritis (RA) subjects with comorbid disorders
NCT00135720	Study of etanercept (Enbrel) in the treatment of pemphigus vulgaris
NCT00144508	Phase III comparative study(open-label) of MRA for rheumatoid arthritis(RA)
NCT00144521	Comparative study (double-blind) of MRA for rheumatoid arthritis (RA)
NCT00144560	Drug-drug interaction study of MRA in patient with rheumatoid arthritis (RA)
NCT00152386	A placebo controlled study to assess efficacy and safety of certolizumab pegol in the treatment of rheumatoid arthritis

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NCT00160602	A study of liquid certolizumab pegol as additional medication to methotrexate in the treatment of signs and symptoms of rheumatoid arthritis and in prevention of joint damage in patients with active rheumatoid arthritis
NCT00160641	A study of the safety and effectiveness of liquid certolizumab pegol in the treatment of signs and symptoms of rheumatoid arthritis and in prevention of joint damage in patients with active rheumatoid arthritis
NCT00160693	Open label long-term safety study of certolizumab pegol (CZP) for patients with rheumatoid arthritis
NCT00162266	Abatacept with methotrexate- phase IIb
NCT00162279	The study of abatacept in combination with etanercept
NCT00175877	A study of the safety and effectiveness of lyophilized certolizumab pegol in the treatment of signs and symptoms of rheumatoid arthritis and in prevention of joint damage in patients with active rheumatoid arthritis
NCT00195494	Study comparing etanercept and methotrexate versus methotrexate alone in rheumatoid arthritis
NCT00195663	Efficacy and safety of adalimumab and methotrexate (MTX) versus MTX monotherapy in subjects with early rheumatoid arthritis
NCT00195702	Efficacy and safety of adalimumab in patients with active rheumatoid arthritis treated concomitantly with methotrexate
NCT00202852	A placebo-controlled, double-blinded, randomized trial of Remicade in Korean patients with rheumatoid arthritis despite methotrexate
NCT00207714	An efficacy and safety study of CNTO 148 subcutaneous injection compared with placebo in patients with active rheumatoid arthritis
NCT00216177	Comparison of adalimumab and infliximab treatment of rheumatoid arthritis
NCT00228839	A Pediatric Phase I Pharmacokinetic Study Using Anti Tumor Necrosis Factor Antibody (Infliximab) for Treatment of Acute Graft Versus Host Disease
NCT00233558	Open-label steroid reduction study of adalimumab with methotrexate in patients with active rheumatoid arthritis
NCT00234845	Adalimumab in combination with methotrexate vs methotrexate alone in early rheumatoid arthritis
NCT00234897	Efficacy of Humira in subjects with active rheumatoid arthritis
NCT00234936	Quality of life study with adalimumab in rheumatoid arthritis
NCT00235859	Adalimumab administered in Korean rheumatoid arthritis subjects treated with methotrexate
NCT00236028	A safety and efficacy study for infliximab (Remicade) with methotrexate in patients with early rheumatoid arthritis
NCT00243412	A study of the safety and efficacy of rituximab in patients with moderate to severe rheumatoid arthritis receiving methotrexate

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NCT00244556	Study comparing Enbrel (etanercept) plus methotrexate versus Enbrel alone in active rheumatoid arthritis despite current methotrexate therapy
NCT00249041	Enbrel liquid immunogenicity protocol
NCT00252668	Study evaluating the combination of etanercept and methotrexate in rheumatoid arthritis subjects
NCT00254293	Study to assess steady-state trough concentrations, safety, and immunogenicity of abatacept after subcutaneous (sc) administration to subjects with rheumatoid arthritis (RA)
NCT00259610	Treatment of early aggressive rheumatoid arthritis (TEAR)
NCT00261118	Rituximab in active ulcerative colitis
NCT00264537	A study of the safety and efficacy of golimumab in subjects with rheumatoid arthritis that are methotrexate-naive
NCT00264550	An efficacy and safety study of golimumab in patients with active rheumatoid arthritis despite methotrexate therapy
NCT00266227	A study of retreatment with rituximab in patients with rheumatoid arthritis receiving background methotrexate
NCT00269867	Infliximab plus methotrexate for the treatment of rheumatoid arthritis
NCT00279734	Vaccination study of abatacept (BMS-188667) for normal healthy volunteers
NCT00279760	Phase I/II multiple-dose LEA29Y vs CTLAG4IG vs placebo in rheumatoid arthritis
NCT00282308	A study to evaluate the effects of rituximab on immune responses in subjects with active rheumatoid arthritis receiving background methotrexate
NCT00283712	Use of infliximab for the treatment of pemphigus vulgaris
NCT00291915	Multicenter randomized prospective trial comparing methotrexate alone or in combination with adalimumab in early arthritis
NCT00293202	Safety and efficacy study of the effect of etanercept in hemodialysis patients
NCT00298272	Safety and tolerability of Rituxan with methotrexate and etanercept or methotrexate and adalimumab in patients with active rheumatoid arthritis
NCT00299104	A study to evaluate rituximab in combination with methotrexate in methotrexate-naive patients with active rheumatoid arthritis
NCT00299130	A study to evaluate the safety and efficacy of rituximab in combination with methotrexate compared to methotrexate alone in patients with active rheumatoid arthritis
NCT00299546	A study of the safety and efficacy of golimumab (CNTO 148) in subjects with active rheumatoid arthritis previously treated with biologic anti-TNFa agent(s)
NCT00317538	Open-label, pilot protocol of patients with rheumatoid arthritis who switch to infliximab after incomplete response to etanercept
NCT00327275	The effects of a 16-week individualized, intensive strength training program in patients with rheumatoid arthritis

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NCT00345748	A study of abatacept in Japanese patients with active rheumatoid arthritis while receiving methotrexate
NCT00361335	A study of safety and effectiveness of golimumab in participants with active rheumatoid arthritis despite methotrexate therapy
NCT00363350	Rituximab treatment in Sjögren's syndrome
NCT00365001	A drug interaction study between tocilizumab, methotrexate and simvastatin on patients with rheumatoid arthritis
NCT00393471	Study comparing etanercept plus methotrexate to either etanercept or methotrexate alone in rheumatoid arthritis
NCT00394589	Re^3 (re-cube: retain Remicade® response)
NCT00396747	A comparison of methotrexate alone or combined to infliximab or to pulse methylprednisolone in early rheumatoid arthritis: a magnetic resonance imaging study
NCT00396812	Rituximab for the treatment of early rheumatoid arthritis (RA)
NCT00405275	Rheumatoid arthritis: comparison of active therapies in patients with active disease despite methotrexate therapy
NCT00409838	A phase III study of abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate
NCT00420199	A phase IIIb study of BMS-188667 in subjects with active rheumatoid arthritis and inadequate response to methotrexate
NCT00420927	Study of the optimal protocol for methotrexate and adalimumab combination therapy in early rheumatoid arthritis
NCT00422227	Study comparing etanercept with usual DMARD therapy in subjects with rheumatoid arthritis in the Asia Pacific region
NCT00422383	A study of retreatment with Mabthera (rituximab) in combination with methotrexate in patients with rheumatoid arthritis (RA)
NCT00424502	A study of Mabthera (rituximab) in patients with rheumatoid arthritis who have had an inadequate response to a TNF-blocker
NCT00425932	Impact of rituximab on MRI evidence of disease activity in patients with moderate to severe rheumatoid arthritis
NCT00426543	Effect of b-cell depletion in patients with primary Sjögren's syndrome
NCT00432406	Tumor necrosis factors (TNF)- blockade for psoriatic arthritis
NCT00442611	A study to evaluate the safety and efficacy of abatacept in patients with diffuse systemic sclerosis (scleroderma)
NCT00443430	Trial of early aggressive drug therapy in juvenile idiopathic arthritis
NCT00443950	Study evaluating the efficacy and safety of etanercept in Chinese subjects with rheumatoid arthritis

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NCT00445770	Study evaluating the efficacy and safety of etanercept and methotrexate in Japanese subjects with rheumatoid arthritis
NCT00459706	Study comparing perceptions and satisfaction for two different delivery mechanisms for etanercept
NCT00462072	Centocor microarray study of patients
NCT00463580	A study of infliximab for treatment resistant major depression
NCT00468377	Safety and efficacy study of re-treatment with rituximab (Mabthera/Rituxan) in patients with active rheumatoid arthritis who respond poorly to anti-TNFa therapies
NCT00468546	A study to evaluate the safety and efficacy of Mabthera (rituximab) in combination with methotrexate (MTX) in participants with active rheumatoid arthritis who failed on anti-tumor necrosis factor alpha therapy
NCT00480272	Prospective study on intensive early rheumatoid arthritis treatment
NCT00484237	A study evaluating 10 mg and 25 mg doses of etanercept in patients with rheumatoid arthritis
NCT00502996	A non-comparative study to assess the safety of Mabthera (rituximab) in patients with rheumatoid arthritis.
NCT00503425	A study of Mabthera (rituximab) in participants with rheumatoid arthritis who have had an inadequate response to disease-modifying antirheumatic drugs (DMARD) and/or anti-tumor necrosis factor (anti-TNF) therapy
NCT00514982	Medical treatment of colitis in patients with Hermansky-Pudlak Syndrome
NCT00520572	A 6-month randomised, double-blind, open arm comparator, phase IIb, with azd9056, in patients with rheumatoid arthritis (RA)
NCT00522184	Intra-articular injection of etanercept in patient suffering from rheumatoid arthritis: a double-blind randomized study
NCT00523692	Remission induction in very early rheumatoid arthritis
NCT00531817	A study of tocilizumab in combination with DMARDs in patients with moderate to severe rheumatoid arthritis
NCT00533897	Phase IIIb subcutaneous missed dose study
NCT00534313	Safety and efficacy of abatacept versus placebo in participants with psoriatic arthritis
NCT00535782	A study of the effect of tocilizumab on markers of atherogenic risk in patients with moderate to severe rheumatoid arthritis
NCT00537667	The spectra study
NCT00538902	Safety and efficacy study of adalimumab in adult Chinese rheumatoid arthritis subjects treated with methotrexate
NCT00544154	Efficacy and safety of CDP870 and methotrexate compared to methotrexate alone in subjects with rheumatoid arthritis

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NCT00548834	Efficacy and safety of CDP870 versus placebo in the treatment of the signs and symptoms of rheumatoid arthritis
NCT00550446	A phase 2 study for patients with a physician's diagnosis of rheumatoid arthritis
NCT00555542	An analysis of peripheral blood t cell subsets on rheumatoid arthritis
NCT00559585	Methotrexate-inadequate response study
NCT00565331	Rituximab for prevention of rejection after renal transplantation
NCT00565409	Study comparing etanercept in combination with methotrexate in subjects with rheumatoid arthritis
NCT00578305	A study of rituximab (Mabthera®/Rituxan®) in patients with rheumatoid arthritis and inadequate response to methotrexate
NCT00578565	Rituximab in rheumatoid arthritis lung disease
NCT00580229	A safety analysis of oral prednisone as a pre-treatment for rituximab in rheumatoid arthritis.
NCT00580840	Dosing flexibility study in patients with rheumatoid arthritis
NCT00595413	Atacicept in anti-tumor necrosis factor alpha-naive subjects with rheumatoid arthritis (AUGUST II)
NCT00647270	Study comparing 80 mg of adalimumab with placebo, and demonstrating the non-inferiority of monthly 80 mg adalimumab dosing compared with 40 mg adalimumab every other week dosing
NCT00647491	A study of adalimumab in adult Japanese subjects with rheumatoid arthritis
NCT00647920	Study of adalimumab administered as subcutaneous injections in adult Chinese rheumatoid arthritis subjects treated with methotrexate
NCT00649545	Study of the human anti-TNF monoclonal antibody in patients with active rheumatoid arthritis
NCT00649922	Assessment of the effect of adalimumab on response to influenza virus and pneumococcal vaccines in subjects with rheumatoid arthritis
NCT00650026	Early access program of the safety of human anti-TNF monoclonal antibody adalimumab in subjects with active rheumatoid arthritis
NCT00650156	Pharmacokinetic and safety study with adalimumab in Chinese subjects with mild rheumatoid arthritis
NCT00650390	Open label study to assess efficacy and safety of the fully human anti-TNF-alpha monoclonal antibody adalimumab
NCT00654368	CAMEO: Canadian methotrexate and etanercept outcome study
NCT00660647	Optimized treatment algorithm for patients with early rheumatoid arthritis (RA)
NCT00664521	Atacicept in combination with rituximab in subjects with rheumatoid arthritis
NCT00674362	Rheumatoid arthritis (RA) moderate to low disease activity study
NCT00678782	Evaluation of the efficacy and safety of intra-articular etanercept in patients with refractory knee joint synovitis

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NCT00683345	Fatigue and interleukin-1 (IL-1) blockade in primary Sjögrens syndrome
NCT00686868	Study to evaluate sc route of administration of ofatumumab in RA patients
NCT00688103	Efficacy and safety of etanercept in active RA despite methotrexate therapy in japan
NCT00689728	A study for patients with rheumatoid arthritis on methotrexate (MTX) with an inadequate response to TNF-inhibitor therapy
NCT00691028	Efficacy and safety of increased dose of ta-650 (infliximab) in patients with rheumatoid arthritis
NCT00696059	Humira in rheumatoid arthritis - do bone erosions heal?
NCT00706797	Study evaluating efficacy/safety of etanercept + methotrexate compared to usual treatment in moderate RA subjects
NCT00711503	Anti-interleukin-1 in diabetes action
NCT00713544	A proof of concept and dose ranging study in patients with rheumatoid arthritis
NCT00714493	RESTART C0168Z05 rheumatoid arthritis study
NCT00716248	Bucillamine study of holding remission after infliximab dose-off
NCT00717236	Certolizumab pegol for the treatment of patients with active rheumatoid arthritis
NCT00720798	An extension study of tocilizumab (myeloma receptor antibody (MRA)) in patients completing treatment in tocilizumab core studies
NCT00721123	A long-term extension study of tocilizumab (myeloma receptor antibody (MRA)) in patients with rheumatoid arthritis
NCT00727987	A safety and efficacy study of golimumab (CNTO 148) in patients with active rheumatoid arthritis despite methotrexate therapy
NCT00732875	A trial of anti-TNF chimeric monoclonal antibody (CA2) in Korean patients with active rheumatoid arthritis despite methotrexate (extension part)(study P05645)(completed)
NCT00740948	Tolerance and efficacy of rituximab in Sjögren's disease
NCT00753454	Open label extension for patients coming from the dosing flexibility study in patients with rheumatoid arthritis (RA)
NCT00754559	A study to assess efficacy with respect to clinical improvement in disease activity and safety of tocilizumab in patients with active rheumatoid arthritis.
NCT00764725	Comparison of MTX+anti-TNF to MTX+conventional DMARDs in patients with early rheumatoid arthritis (RA) who failed MTX alone (SWEFOT)
NCT00768053	Evaluation of EULAR-RAID score in rheumatoid arthritis patients
NCT00771251	A safety and efficacy study of golimumab (CNTO148) in patients with active rheumatoid arthritis (RA)
NCT00773461	A study of tocilizumab in combination with DMARD therapy in patients with active rheumatoid arthritis

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NCT00780793	Spacing of TNF-blocker injections in rheumatoid arthritis study
NCT00783536	A multicenter study to compare the efficacy and safety of the combination of etanercept and methotrexate in treatment of rheumatoid arthritis
NCT00789724	Anakinra to prevent post-infarction remodeling
NCT00791921	Efficacy confirmation trial of CDP870 without coadministration of methotrexate (MTX) in Japanese rheumatoid arthritis (RA)
NCT00791999	Efficacy confirmation trial of CDP870 as add-on medication to methotrexate (MTX) in Japanese rheumatoid arthritis (RA)
NCT00794898	Efficacy of Remicade in the treatment of active rheumatoid arthritis despite methotrexate (study p03027)
NCT00796705	Switching anti-TNF-alpha agents in rheumatoid arthritis (RA)
NCT00808210	A study to evaluate ocrelizumab in combination with methotrexate compared with infliximab plus methotrexate in patients with active rheumatoid arthritis currently responding inadequately to etanercept or adalimumab
NCT00808509	A pilot study of the feasibility of discontinuation of adalimumab in stable rheumatoid arthritis patients in clinical remission
NCT00810199	A study of tocilizumab and methotrexate treatment strategies (adding tocilizumab to methotrexate versus switching to tocilizumab) in patients with active rheumatoid arthritis with inadequate response to prior methotrexate treatment
NCT00810277	A study of tocilizumab in patients with rheumatoid arthritis who have an inadequate response to current non-biologic DMARDs
NCT00814866	Bone resorption, osteoclastogenesis and adalimumab
NCT00837434	Anti-TNF agents for the treatment of rheumatoid arthritis
NCT00843778	Follow-up of rheumatoid arthritis (RA) moderate to low disease activity study
NCT00844714	Cardiovascular risk markers in patients with rheumatoid arthritis: effect of rituximab therapy
NCT00845832	A study of combination treatment with Mabthera (rituximab) and Roactemra (tocilizumab) versus Roactemra in patients with rheumatoid arthritis with an incomplete response to methotrexate
NCT00848354	Open-label study comparing etanercept to conventional disease modifying antirheumatic drug (DMARD) therapy
NCT00850343	Long-term treatment study of certolizumab pegol without coadministration of methotrexate in Japanese rheumatoid arthritis (RA) patients
NCT00851318	Long-term treatment study of certolizumab pegol (cdp870) as add-on medication to methotrexate in Japanese rheumatoid arthritis (RA) patients
NCT00853385	A phase 3 study comparing 2 doses of CP-690,550 and the active comparator, Humira (adalimumab) versus Placebo for treatment of rheumatoid arthritis
NCT00858780	Study comparing the effect on disease activity when reducing or discontinuing etanercept in subjects with RA

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NCT00868751	Single patient use of tocilizumab in systemic onset juvenile idiopathic arthritis
NCT00870467	A study of adalimumab in Japanese subjects with rheumatoid arthritis
NCT00887341	A study comparing infusion rates of tocilizumab in patients with moderate to severe rheumatoid arthritis
NCT00891020	A study of tocilizumab in patients with moderate to severe active rheumatoid arthritis who have an inadequate response to or are unable to tolerate biologic and non-biologic disease-modifying antirheumatic drugs (DMARDs)
NCT00901550	The Chinese university of Hong Kong early arthritis study
NCT00908089	Tnf-blocking therapy in combination with disease-modifying antirheumatic drugs in early rheumatoid arthritis
NCT00913458	Study evaluating etanercept plus methotrexate in early rheumatoid arthritis
NCT00920478	Targeting synovitis in early rheumatoid arthritis
NCT00929864	Abatacept versus adalimumab head-to-head
NCT00948610	Sleep and immunity in rheumatoid arthritis: Remicade substudy
NCT00963703	Treatment of TNFa naive patients with poor prognosis rheumatoid arthritis
NCT00965653	A study of subcutaneously administered tocilizumab in patients with rheumatoid arthritis
NCT00973479	An effectiveness and safety study of intravenous golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate therapy
NCT00977106	Torpedo study: a study on rapid effect of tocilizumab in patients with rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs (DMARDs) or anti-TNF
NCT00979771	A study to investigate the ability of GSK706769 to maintain clinical remission after withdrawal of Enbrel in rheumatoid arthritis patients
NCT00989235	Substudy - low dose of abatacept in subjects with rheumatoid arthritis
NCT00993317	A study of cdp870 as add-on meditation to methotrexate (MTX) in patients with rheumatoid arthritis
NCT00993668	Assessing the use of certolizumab pegol in adult subjects with rheumatoid arthritis on the antibody response when receiving influenza virus and pneumococcal vaccines
NCT00996606	A study of tocilizumab in combination with disease-modifying anti-rheumatic drugs (DMARDs) in participants with moderate to severe active rheumatoid arthritis with an inadequate response to DMARDs
NCT01000441	Rotation or change of biotherapy after first anti-TNF treatment failure for rheumatoid arthritis
NCT01001832	Efficacy, pharmacokinetics, safety, and immunogenicity study of abatacept administered subcutaneously to treat rheumatoid arthritis in Japanese patients
NCT01002781	Efficacy and safety of tocilizumab in adult's still disease

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NCT01004432	Golimumab in rheumatoid arthritis participants with an inadequate response to etanercept (Enbrel) or adalimumab (Humira)
NCT01007435	A study of tocilizumab as monotherapy and in combination with methotrexate versus methotrexate in patients with early moderate to severe rheumatoid arthritis
NCT01009879	Human tumor necrosis factor alpha (TNFa)-induced pre-B cell bone marrow emigrants
NCT01010503	A study of tocilizumab with or without methotrexate in patients with rheumatoid arthritis
NCT01021735	Optimal management of rheumatoid arthritis patients requiring biologic therapy
NCT01033656	Treatment of refractory adult-onset Still's disease with anakinra: a randomized study
NCT01034137	A study of tocilizumab and methotrexate in combination or as monotherapy in treatment-naïve patients with early rheumatoid arthritis
NCT01034397	A study of tocilizumab plus non-biological DMARD in patients with moderate to severe rheumatoid arthritis and an inadequate response to non-biological DMARDs
NCT01044498	A study of tocilizumab in combination with an oral contraceptive in patients with rheumatoid arthritis
NCT01072058	Heart function in rheumatoid arthritis and ankylosing spondylitis pre and post-TNF blocker
NCT01086033	A 3-year study following up patients with moderate to severe rheumatoid arthritis treated with Humira in Greece
NCT01088165	The influence of adalimumab on cardiovascular and metabolic risk in psoriasis
NCT01101555	Repeat dose subcutaneous Rheumatoid arthritis efficacy study
NCT01116427	A cooperative clinical study of abatacept in multiple sclerosis
NCT01117129	A study of efficacy of rituximab (Mabthera/Rituxan) in patients with rheumatoid arthritis using magnetic resonance imaging of the hand (RESONAR)
NCT01119859	A study of tocilizumab (roactemra/Actemra) versus adalimumab in patients with rheumatoid arthritis
NCT01120366	Success of tocilizumab in RA patients with remission induction and sustained efficacy after discontinuation
NCT01123070	Tl011 in severe, active rheumatoid arthritis patients
NCT01126541	SMART Study: a study of re-treatment with Mabthera (rituximab) in patients with rheumatoid arthritis who have failed on anti-TNF alfa therapy
NCT01142726	Efficacy and safety study of abatacept subcutaneous plus methotrexate in inducing remission in adults with very early rheumatoid arthritis
NCT01147341	Can TNF-alpha incomplete secondary responders attain a safe and efficacious response switching to Cimzia
NCT01162421	A Canadian study to evaluate early use of adalimumab after methotrexate failure in early rheumatoid arthritis

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NCT01163617	The usability and injection time of the Physiolis syringe and autoinjector in rheumatoid arthritis patients
NCT01163747	A study of the effects of Roactemra/Actemra on vaccination in patients with rheumatoid arthritis on background methotrexate (VISARA)
NCT01173120	Methotrexate - inadequate response device sub-study
NCT01185288	A study to determine the effect of methotrexate (MTX) dose on clinical outcome and ultrasonographic signs in subjects with moderately to severely active rheumatoid arthritis (RA) treated with adalimumab (MUSICA)
NCT01185301	Study to determine the effects of different doses of methotrexate (MTX) when taken with adalimumab in subjects with early rheumatoid arthritis (RA)
NCT01185522	An observational study of the impact of Roactemra/Actemra on fatigue in patients with rheumatoid arthritis (PEPS)
NCT01194414	A study to compare subcutaneous versus intravenous administration of Roactemra/Actemra (tocilizumab) in participants with moderate to severe active rheumatoid arthritis
NCT01197066	Open-label, extension study of CDP870 in patients with rheumatoid arthritis
NCT01197144	Pain modulation in rheumatoid arthritis (RA) - influence of adalimumab
NCT01211834	Efficacy and safety of tocilizumab in combination with DMARDs in patients with moderate to severe rheumatoid arthritis
NCT01212094	Double blind combination of rituximab by intravenous and intrathecal injection versus placebo in patients with low-inflammatory secondary progressive multiple sclerosis (RIVITALISE)
NCT01213017	The effect of certolizumab pegol on MRI synovitis and bone edema in rheumatoid arthritis patients
NCT01216631	Seronegative oligoarthritis of the knee study (SOKS)
NCT01217086	Program evaluating the autoimmune disease investigational drug ct-p13 in RA patients (PLANETRA)
NCT01221636	Pharmacokinetic study to compare the blood levels of low vs high metal manufacture of abatacept
NCT01225393	A study to evaluate the efficacy and safety of MLTA3698A in combination with a disease-modifying anti-rheumatic drug (DMARD) compared with adalimumab in combination with a DMARD in patients with active rheumatoid arthritis
NCT01232569	A study of Roactemra/Actemra (tocilizumab) given subcutaneously in combination with traditional DMARDs in patients with moderate to severe active rheumatoid arthritis
NCT01235598	Magnetic resonance image verified early response to certolizumab pegol in subjects with active rheumatoid arthritis (RA)
NCT01242488	Efficacy and safety of CDP6038 in patients with rheumatoid arthritis with an unsuccessful response to anti-tumor necrosis factor (anti-TNF) therapy
NCT01244958	Addition of rituximab to leflunomide in patients with active rheumatoid arthritis
NCT01245361	A 6-months infliximab or placebo study in UA at high risk of RA: clinical, radiological and synovial benefit

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NCT01245439	A study of Roactemra/Actemra (tocilizumab) in patients with moderate to severe rheumatoid arthritis
NCT01245452	Study of the response and cardiorespiratory endurance in early RA patients treated with tocilizumab or methotrexate
NCT01248780	Study of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite methotrexate therapy
NCT01251120	A study of Roactemra/Actemra (tocilizumab) in combination with DMARDs versus current best practice DMARD therapy in patients with rheumatoid arthritis
NCT01255761	A comparison of two assessment tools in predicting treatment success of Cimzia in rheumatoid arthritis subjects
NCT01258712	Study of tocilizumab in combination with methotrexate for treatment of moderate to severe rheumatoid arthritis patients
NCT01264770	Evaluation of efficacy and safety of Fostamatinib monotherapy compared with adalimumab monotherapy in patients with rheumatoid arthritis (RA)
NCT01270035	Efficacy and safety of adalimumab 80 mg every other week with methotrexate
NCT01270087	The effect of adalimumab (Humira) on vascular abnormalities in rheumatoid arthritis. A pilot study
NCT01270997	Randomized double-blind parallel trial to evaluate equivalence in efficacy and safety of hd203 and Enbrel in RA patients
NCT01272908	A study of Mabthera (rituximab) in patients with rheumatoid arthritis who have failed on one prior anti-TNF therapy (reset)
NCT01274182	Gp2013 in the treatment of RA patients refractory to or intolerant of standard therapy
NCT01283971	A study of Roactemra/Actemra (tocilizumab) versus adalimumab in combination with methotrexate (MTX) in patients with moderate to severe active rheumatoid arthritis and an inadequate response to treatment with only one tumor necrosis factor (TNF)-inhibitor
NCT01292265	A 12 week study to assess changes in joint inflammation using ultrasonography in patients with rheumatoid arthritis (RA)
NCT01295151	SWITCH clinical trial for patients with rheumatoid arthritis who have failed an initial TNF-blocking drug
NCT01295814	Efficacy study of adalimumab to treat interstitial cystitis
NCT01303874	Etanercept and methotrexate in patients to induce remission in early arthritis (empire)
NCT01308255	Infliximab as induction therapy in early rheumatoid arthritis (idea)
NCT01313208	Moderate rheumatoid arthritis (RA) with etanercept (Enbrel)
NCT01313520	A study to evaluate the effectiveness of infliximab and changes in hand and wrist magnetic resonance imaging (MRI) in participants with active rheumatoid arthritis (RA) (p08136)
NCT01326962	A study of Roactemra/Actemra (tocilizumab) in patients with rheumatoid arthritis who have an inadequate response to DMARDs or anti-TNF

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NCT01331837	A study of tocilizumab in comparison to etanercept in participants with rheumatoid arthritis and cardiovascular disease risk factors
NCT01333878	Impact of subcutaneous abatacept in rheumatoid arthritis assessing inhibition of structural damage
NCT01338103	Treatment of pemphigus patients with rituximab 1000mgx2 and assessment of immune status via Cylex
NCT01350804	Efficacy at 24 weeks and safety, tolerability and long term efficacy of secukinumab (ain457) in patients with active rheumatoid arthritis (RA) and an inadequate response to anti-tumor necrosis factor α (Anti-TNFα) agents (CAIN457f2309 and CAIN457f2309e1)
NCT01351480	Benefits of injectable abatacept using magnetic resonance imaging (MRI) in rheumatoid arthritis (RA) patients
NCT01362153	A pharmacokinetic (pk) and pharmacodynamic (pd) study of golimumab in patients with rheumatoid arthritis (RA)
NCT01369017	Effect of interleukin-1 receptor antagonist on inhalation of 20,000 EU clinical CTR reference endotoxin in normal volunteers
NCT01373151	Phase IIB rheumatoid arthritis dose ranging study for BMS-945429 in subjects who are not responding to methotrexate
NCT01374971	Rheumatoid arthritis treatment and biopsy study assessing certolizumab pegol (Cimzia)
NCT01382160	Serum concentration of adalimumab as a predictive factor of clinical outcomes in rheumatoid arthritis (AFORA)
NCT01390441	A study of the pharmacokinetics and safety of mk-8808 (MK-8808-002)
NCT01390545	Velvet, a dose range finding trial of veltuzumab in subjects with moderate to severe rheumatoid arthritis
NCT01394913	Comparison of two etanercept regimens (Reumatocept® versus Enbrel®) for treatment of rheumatoid arthritis
NCT01396317	Study of tocilizumab to treat polymyalgia rheumatica
NCT01399697	A study of Roactemra/Actemra (tocilizumab) in combination with methotrexate versus Roactemra/Actemra monotherapy in patients with rheumatoid arthritis and an inadequate response to methotrexate
NCT01405326	Restore Working Ability in rheumatoid arthritis
NCT01426815	Exploration of TNF-alpha blockade with golimumab in the induction of clinical remission in patients with early peripheral spondyloarthritis (SPA) according to ASAS-criteria
NCT01439204	Pharmacokinetic study to compare the blood levels of abatacept manufactured at Lonza biologics to the blood levels of abatacept manufactured at the Devens, Massachusetts (MA) facility of Bristol-Myers Squibb
NCT01443364	Open label study to assess the predictability of early response to certolizumab pegol in patients with rheumatoid arthritis
NCT01451203	Efficacy confirmation study of cdp870 in early rheumatoid arthritis

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NCT01468077	A study in patients with moderate to severe active rheumatoid arthritis comparing different infusion durations of Roactemra/Actemra (tocilizumab) treatment
NCT01491815	Active conventional therapy compared to three different biologic treatments in early rheumatoid arthritis with subsequent dose reduction
NCT01500278	Study to assess the short- and long-term efficacy of certolizumab pegol plus methotrexate compared to adalimumab plus methotrexate in subjects with moderate to severe rheumatoid arthritis (RA) inadequately responding to methotrexate
NCT01502423	A crossover study of the safety and tolerability of two formulations of adalimumab
NCT01519791	A multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in combination with methotrexate in the treatment of disease modifying antirheumatic drugs (DMARD)-naïve adults with early active rheumatoid arthritis
NCT01521923	A multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in combination with methotrexate in the treatment of disease modifying antirheumatic drugs (DMARD)-naïve adults with early active rheumatoid arthritis
NCT01526057	A pharmacokinetic/pharmacodynamic study comparing pf-05280586 to rituximab in subjects with active rheumatoid arthritis with an inadequate response to TNF inhibitors (reflections b328-01)
NCT01534884	Demonstrate the equivalence of ct-p10 to Mabthera with respect to the pharmacokinetic profile in patients with rheumatoid arthritis
NCT01548768	RHYTHM (formerly Escape II Myocardium)
NCT01557374	Toward the lowest effective dose of abatacept or tocilizumab
NCT01561313	Crossover study of safety and tolerability of two formulations of adalimumab
NCT01566201	Effects of interleukin-1 inhibition on vascular and left ventricular function in rheumatoid arthritis patients with coronary artery disease
NCT01567358	Study of ni-071 in comparison with Remicade in patients with rheumatoid arthritis
NCT01571219	An extension study to demonstrate long-term efficacy and safety of CT-P13 when co-administered with methotrexate in patient with rheumatoid arthritis who were treated with infliximab (Remicade or CT-P13) in study CT-P13 3.1
NCT01578850	Study conducted in subjects with rheumatoid arthritis who have moderate to severe disease activity despite methotrexate therapy with or without other non biologic disease modifying antirheumatic drugs (DMARDs)for at least 12 weeks prior to screening
NCT01587989	A study of Roactemra/Actemra (tocilizumab) with or without methotrexate in patients with mild to moderate rheumatoid arthritis with an inadequate response to methotrexate
NCT01590966	Scintigraphic detection of the biodistribution of tumor necrosis factor with a radiolabeled anti-TNF in patients with active rheumatoid arthritis and active axial and peripheral spondyloarthritis
NCT01602302	Ultrasound and withdrawal of biological DMARDs in rheumatoid arthritis
NCT01609205	Doppler evaluation in RA patients after adalimumab
NCT01635686	Comparison the safety and pharmacokinetic characteristics of DWP422 25 mg with those of Enbrel 25MG PFS inj. after subcutaneous injection in healthy male volunteers

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NCT01638715	A randomized, multi-center biomarker trial to predict therapeutic responses of patients with rheumatoid arthritis to a specific biologic mode of action
NCT01643928	Rheumatoid arthritis extension trial for subjects who have participated in other PF-05280586 trials (reflections b328-04)
NCT01649804	A long-term safety extension study of WA19926 in participants with rheumatoid arthritis
NCT01657513	TNF-alfa inhibitors and antibody production in patients with psoriasis
NCT01661140	A study of Roactemra/Actemra (tocilizumab) in combination with methotrexate in patients with severe active rheumatoid arthritis, comparing tapering versus maintaining the methotrexate dosage
NCT01664598	An extension study of wa19926 of the long-term safety of Roactemra/Actemra (tocilizumab) in patients with early moderate to severe rheumatoid arthritis
NCT01665430	A long-term extension study to wa19926 of Roactemra/Actemra (tocilizumab) in patients with early, moderate to severe rheumatoid arthritis
NCT01668966	A long term extension study of wa19926 (nct01649804) of tocilizumab (Roactemra/Actemra) in participants with early moderate to severe rheumatoid arthritis
NCT01682512	Efficacy, pharmacokinetics, and safety of bi 695500 in patients with rheumatoid arthritis
NCT01690299	Phase 3b safety and efficacy study of apremilast to treat moderate to severe plaque-plaque psoriasis
NCT01696929	An open-label trial of tocilizumab in schizophrenia
NCT01710358	A study in moderate to severe rheumatoid arthritis
NCT01712178	A study in rheumatoid arthritis (RA) patients to compare two formulations of adalimumab for pharmacokinetic, pharmacodynamic and safety
NCT01715831	A long-term safety extension study of tocilizumab in Brazilian participants with RA having completed the studies ml21530 and ma21488
NCT01715896	A study of mavrilimumab versus anti tumor necrosis factor in subjects with rheumatoid arthritis
NCT01717859	Musculoskeletal ultrasound in predicting early dose titration with tocilizumab
NCT01724268	Corticosteroids and anti TNF in methotrexate inadequate responder rheumatoid arthritis patient
NCT01730456	A long-term extension study of Roactemra/Actemra (tocilizumab) in patients with early moderate to severe rheumatoid arthritis who completed study WA19926
NCT01734993	A long-term extension study of WA22762 to evaluate safety and efficacy of subcutaneous tocilizumab in participants with moderate to severe rheumatoid arthritis (RA)
NCT01752335	Effect of monoclonal anti-il6 antibody (tocilizumab) on the cardiovascular risk in patients with rheumatoid arthritis
NCT01752855	Study in rheumatoid arthritis for subjects who completed preceding study M13-390 with adalimumab
NCT01758198	Abatacept post-marketing clinical study in Japan

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NCT01759030	Study of safety and efficacy of BCD-020 comparing to Mabthera in patients with rheumatoid arthritis
NCT01764997	An evaluation of sarilumab plus methotrexate compared to etanercept plus methotrexate in RA patients not responding to adalimumab plus methotrexate
NCT01765374	Study of sonographic efficacy of rituximab in rheumatoid arthritis
NCT01768572	To evaluate the safety of SAR153191 (REGN88) and tocilizumab added to other RA drugs in patients with RA who are not responding to or intolerant of anti-TNF therapy (SARIL-RA-ASCERTAIN)
NCT01772316	A long-term extension study of wa22763 and na25220 of subcutaneous Roactemra/Actemra (tocilizumab) in patients with moderate to severe rheumatoid arthritis
NCT01782235	Efficacy of tocilizumab in primary Sjögren's syndrome
NCT01783015	Study of etanercept in subjects with rheumatoid arthritis who have had an inadequate response to adalimumab or infliximab plus methotrexate
NCT01793519	Stopping TNF alpha inhibitors in rheumatoid arthritis
NCT01794117	Anakinra for inflammatory pustular skin diseases
NCT01835613	Evaluation effects of treatment with il-6r inhibitor on clinical response and biomarkers in patients with rheumatoid arthritis (RA) not responding to DMARDs and/or a first biological agent
NCT01842386	Rituximab for anti-cytokine autoantibody-associated diseases
NCT01844895	Methotrexate-inadequate response autoinjector device sub study
NCT01846975	Introducing a single iv abatacept treatment in RA patients currently receiving weekly sc abatacept to simulate a holiday
NCT01855789	A study of the impact of methotrexate (MTX) discontinuation on the efficacy of subcutaneous tocilizumab with methotrexate in participants with moderate to severe active rheumatoid arthritis
NCT01864265	Prediction of response to certolizumab pegol treatment by functional MRI of the brain
NCT01873443	Long-term efficacy and safety of ct-p10 in patients with RA
NCT01875991	Preference between two autoinjectors in patients with rheumatoid arthritis and plaque psoriasis treated with etanercept
NCT01878318	A study of the effect of Roactemra/Actemra (tocilizumab) in combination with methotrexate on articular damage in the hand in patients with moderate to severe rheumatoid arthritis who have an inadequate response to non-biological DMARDs
NCT01890473	Study to characterize the pharmacokinetics of a single dose of sc abatacept 125 mg using the bd autoinjector or the prefilled syringe
NCT01893996	Study of adalimumab to lower cardiovascular risk in RA patients with well controlled joint disease
NCT01895309	A study comparing sb4 to Enbrel® in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy
NCT01901185	Study to evaluate the ability of subjects with rheumatoid arthritis or psoriatic arthritis to effectively use a reusable autoinjector to self-inject etanercept

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NCT01927263	A phase 3 study of ni-071 in patients with rheumatoid arthritis
NCT01927757	Evaluating etanercept use in patients with moderate to severe rheumatoid arthritis who have lost response to adalimumab
NCT01936181	A study comparing SB2 to Remicade® in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy
NCT01941095	A study of subcutaneously administered Roactemra/Actemra (tocilizumab) in patients with rheumatoid arthritis
NCT01941940	A study to evaluate efficacy of tocilizumab administered as monotherapy or in combination with methotrexate and/or other disease modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) participants
NCT01951170	An open-label study of Roactemra/Actemra (tocilizumab) in patients with moderate to severe active rheumatoid arthritis
NCT01954979	A phase i study of abatacept in the treatment of patients with steroid refractory chronic graft versus host disease (CGVHD)
NCT01962974	A golimumab phase 3b, multicenter, assessment of intravenous efficacy in rheumatoid arthritis subjects who have diminished disease control despite treatment with infliximab (Remicade®)
NCT01969409	Autoantibody reduction therapy in patients with idiopathic pulmonary fibrosis
NCT01970475	Efficacy and safety study of ABP 501 compared to adalimumab in subjects with moderate to severe rheumatoid arthritis
NCT01987479	The safety and efficacy of Roactemra/Actemra alone or in combination with non-biologic antirheumatics in rheumatoid arthritis patients
NCT01999868	Efficacy of ustekinumab followed by abatacept for the treatment of psoriasis vulgaris
NCT02001987	A study of Roactemra/Actemra (tocilizumab) in tocilizumab-naive patients with rheumatoid arthritis with inadequate response to non-biologic disease-modifying antirheumatic drugs (DMARDs) or biologic therapy
NCT02010216	A study of Roactemra/Actemra (tocilizumab) in adult patients with rheumatoid arthritis (SVOBODA Programme)
NCT02018042	An open-label single-arm clinical trial to evaluate the efficacy of abatacept in moderate to severe patch type alopecia areata
NCT02019472	A study comparing sirukumab (CNTO 136) monotherapy with adalimumab (Humira®) monotherapy in the treatment of active rheumatoid arthritis
NCT02019602	A multicenter, postmarketing study evaluating the transfer of Cimzia from the mother to the infant via the placenta
NCT02027298	Abatacept for patients with inflammatory arthritis associated with Sjögren's syndrome: an open-label phase II study
NCT02035800	Bone resorption, osteoclastogenesis and adalimumab
NCT02053727	Abatacept vs placebo in RA patients with hepatitis B on entecavir background

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NCT02056184	Targeted ultrasound in rheumatoid arthritis
NCT02067910	Efficacy and safety of abatacept in patients with primary Sjögren's syndrome
NCT02079532	A study of Mabthera (rituximab) in patients with rheumatoid arthritis who have had an inadequate response to a single anti-TNF inhibitor
NCT02090101	Study evaluating the influence of lv5fu2 bevacizumab plus anakinra association on metastatic colorectal cancer
NCT02092467	Safety study of tofacitinib versus tumor necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis
NCT02092961	Randomised double-blind, placebo-controlled, parallel group study in patients with active rheumatoid arthritis: magnetic resonance imaging sub-study
NCT02097264	A trial investigating the mechanism of action of NNC0109-0012 (anti-IL-20 MAB) through synovial biopsies in subjects with rheumatoid arthritis and an inadequate response to methotrexate
NCT02097524	Single-dose study to describe the pharmacodynamics (pd) and safety of sarilumab (regn88/sar153191) and tocilizumab in adults with rheumatoid arthritis (RA)
NCT02097745	A study of the efficacy and safety of re-treatments with rituximab in patients with active rheumatoid arthritis who have had an inadequate response to anti-TNFa therapies
NCT02109289	Etanercept in rheumatoid arthritis and vascular inflammation
NCT02114931	Long-term safety and efficacy of ABP 501 in subjects with moderate to severe rheumatoid arthritis
NCT02115750	Comparison of CHS-0214 to Enbrel (etanercept) in patients with rheumatoid arthritis (RA)
NCT02116504	Anti-biopharmaceutical immunization: prediction and analysis of clinical relevance to minimize the risk of immunization in rheumatoid arthritis patients or juvenile idiopathic arthritis patients
NCT02132234	Effects of biological treatment on blood pressure and endothelial function in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis
NCT02137226	BI 695501 compared to adalimumab in patients with active rheumatoid arthritis
NCT02141997	A study to investigate the safety and efficacy of ABT-122 given with methotrexate in subjects with active rheumatoid arthritis who have an inadequate response to methotrexate
NCT02148640	The NOR-SWITCH study
NCT02148718	Rapidity of response to adalimumab treatment in patients with Crohn's disease
NCT02149121	Pk similarity prospective phase 3 study in patients with rheumatoid arthritis
NCT02150473	The effect of adalimumab plus methotrexate (MTX) versus placebo plus MTX on cartilage in (RA) patients
NCT02151851	A study of certolizumab pegol as additional therapy in Chinese patients with active rheumatoid arthritis
NCT02154425	A multicenter, postmarketing study evaluating the concentration of Cimzia® in mature breast milk of lactating mothers

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NCT02167139	A study comparing SB5 to Humira® in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy
NCT02175056	A dose-block randomized, placebo controlled (double-blind), active controlled(open-label), dose-escalation study
NCT02187055	An efficacy and safety study evaluating tofacitinib with and without methotrexate compared to adalimumab with methotrexate
NCT02198651	A phase 4 trial assessing the impact of residual inflammation detected via imaging techniques, drug levels and patient characteristics on the outcome of dose tapering of adalimumab in clinical remission rheumatoid arthritis (RA) subjects (PREDICTRA)
NCT02222493	A study of pf-06438179 (infliximab-Pfizer) and infliximab in combination with methotrexate in subjects with active rheumatoid arthritis
NCT02232880	Treatment of resistant hypertension by prevention of t-cell co-stimulation
NCT02236481	Clinical study to evaluate the efficacy of anakinra in patients with rheumatoid arthritis and diabetes
NCT02242474	Anti-TNF use during elective foot and ankle surgery in patients with rheumatoid arthritis
NCT02260791	A study to compare FKB327 efficacy and safety with Humira® in rheumatoid arthritis patients
NCT02287922	A phase IIb study for alx-0061 monotherapy in subjects with rheumatoid arthritis
NCT02293590	Rice: remission by intra-articular injection plus certolizumab
NCT02296775	Comparative pharmacokinetic, pharmacodynamic, safety and efficacy study of three anti-cd20 monoclonal antibodies in patients with moderate to severe rheumatoid arthritis
NCT02304354	Relationship between t lymphocytes depletion and clinical response to rituximab in rheumatoid arthritis (Lyritux)
NCT02308163	A study to evaluate safety and efficacy of asp015k in patients with rheumatoid arthritis (RA) who had an inadequate response to DMARDs
NCT02319642	An open-label extension study of certolizumab pegol in Chinese patients with rheumatoid arthritis who enrolled in RA0044
NCT02332590	Efficacy and safety of sarilumab and adalimumab monotherapy in patients with rheumatoid arthritis (SARIL-RA-MONARCH)
NCT02353780	Mechanistic studies of b- and t-cell function in RA patients treated with TNF antagonists, tocilizumab, or abatacept
NCT02357069	A study comparing lbec0101 to Enbrel® in subjects with active rheumatoid arthritis despite methotrexate therapy
NCT02371096	Comparative pharmacokinetic trial of rgb-03 and Mabthera
NCT02373813	Study of etanercept monotherapy vs methotrexate monotherapy for maintenance of rheumatoid arthritis remission
NCT02374021	Treatments against RA and effect on FDG-PET/CT

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NCT02376335	B-cell depleting therapy (rituximab) as a treatment for fatigue in primary biliary cirrhosis
NCT02378506	Study to assess the immunogenicity, safety, and efficacy of high capacity process etanercept in rheumatoid arthritis subjects
NCT02393378	Namilumab vs adalimumab in participants with moderate to severe early rheumatoid arthritis inadequately responding to methotrexate
NCT02404558	Single-dose study to describe the safety of sarilumab and tocilizumab in patients with rheumatoid arthritis
NCT02405780	A study to compare FKB327 long-term safety, efficacy and immunogenicity with Humira® in rheumatoid arthritis patients
NCT02429934	Abatacept for SLE arthritis
NCT02430909	Multiple dose study of ucb4940 as add-on to certolizumab pegol in subjects with rheumatoid arthritis
NCT02433184	Very early versus delayed etanercept in patients with RA
NCT02451839	An observational study of the effectiveness of adalimumab on health and disability outcomes in New Zealand patients with immune-mediated inflammatory diseases (VITALITY)
NCT02466581	Dose reduction for early rheumatoid arthritis patients with low disease activity
NCT02468791	MabionCD20® compared to Mabthera® in patients with rheumatoid arthritis
NCT02480153	A study of PF-06410293 (adalimumab-Pfizer) and adalimumab (Humira) In combination with methotrexate in subjects with active rheumatoid arthritis (REFLECTIONS B538-02)
NCT02481180	Tolerance, pharmacokinetics and preliminary efficacy of t0001 in RA (rheumatoid arthritis)
NCT02495129	Study of pharmacodynamic effects of vay736 in patients with primary Sjögren's syndrome
NCT02504268	Effects of abatacept in patients with early rheumatoid arthritis
NCT02514772	Gp2013 treatment in patients with active rheumatoid arthritis, previously treated with Rituxan® or Mabthera®
NCT02526992	Evaluation by HR-pqct of bone microarchitecture changes in patients with rheumatoid arthritis under anti-TNF therapy
NCT02547493	Vaccination against pneumococcal in naïve abatacept rheumatoid arthritis patients
NCT02557100	Study to assess changes in the immune profile in adults with early rheumatoid arthritis
NCT02565810	An multicentre clinical study to evaluate the usability and safety of the pre-filled pen and pre-filled syringe of SB5 in subjects with rheumatoid arthritis
NCT02573012	Study to compare the efficacy of tocilizumab with or without glucocorticoid discontinuation in rheumatoid arthritis participants
NCT02616380	Real-world outcome of adalimumab on rheumatoid arthritis patients in Taiwan
NCT02629159	A study comparing ABT-494 to placebo and to adalimumab in subjects with rheumatoid arthritis who are on a stable dose of methotrexate and who have an inadequate response to methotrexate

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NCT02631538	Safety and efficacy study of subcutaneous belimumab and intravenous rituximab co-administration in subjects with primary Sjögren's syndrome
NCT02638259	Comparative efficacy and safety study of gp2015 and Enbrel® in patients with rheumatoid arthritis
NCT02640612	Long-term assessment of safety and efficacy of BI 695501 in patients with rheumatoid arthritis
NCT02652273	Inhibition of co-stimulation in rheumatoid arthritis
NCT02659150	Effect of subcutaneous Actemra on inflamed atherosclerotic plaques in patients with rheumatoid arthritis
NCT02682823	Tocilizumab real-life human factors (RLHFS) validation study
NCT02683564	Bow015 (infliximab-epirus) and infliximab in patients with active rheumatoid arthritis: the uniform study
NCT02693210	A study to evaluate the efficacy and safety of Mabthera alone and in combination with either cyclophosphamide or methotrexate in patients with rheumatoid arthritis
NCT02714634	Clinical trial evaluating methotrexate + biologic versus methotrexate, salazopyrine and hydroxychloroquine in patients with rheumatoid arthritis and insufficient response to methotrexate
NCT02714881	Lipids, inflammation, and CV risk in RA
NCT02715908	A study to evaluate the long-term safety and efficacy of lbec0101 in subjects with active rheumatoid arthritis despite methotrexate (MTX)
NCT02722044	Usability of an AI for M923 in subjects with moderate to severe RA
NCT02722694	A phase 3 study of abatacept in Chinese patients with active rheumatoid arthritis and inadequate response to methotrexate
NCT02731560	Rituximab (rtx) for disease modifying anti rheumatic drug (DMARD) non-responders in Pakistan: the Pakistan rituximab study (PaRiS)
NCT02743390	Effects of the TNF-alpha inhibitIon on hemodynamic parameters in resistant hypertension
NCT02744196	Clinical trial to evaluate efficacy and safety of Acellbia® (JSC "Biocad") with methotrexate in first line biological therapy of patients with active rheumatoid arthritis
NCT02744755	Clinical trial to compare treatment with GP2017 and Humira® in patients with rheumatoid arthritis
NCT02746380	A study comparing LBAL to Humira® in subjects with active rheumatoid arthritis despite methotrexate therapy
NCT02760407	Evaluation of the effectiveness and safety of two dosing regimens of Olokizumab (OKZ), compared to placebo and adalimumab, in subjects with rheumatoid arthritis (RA) who are taking methotrexate but have active disease
NCT02762838	Comparative clinical trial of efficacy and safety of BCD-055 and Remicade® in combination with methotrexate in patients with active rheumatoid arthritis
NCT02765074	Filling bone erosions: a longitudinal multicentric HR-PQCT study of subcutaneous tocilizumab in rheumatoid arthritis
NCT02770794	Optimization of infliximab withdrawal strategy for rheumatoid arthritis

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NCT02778906	Abatacept reversing subclinical inflammation as measured by MRI in ACPA positive arthralgia
NCT02779114	Retro (reduction of therapy in RA patients in ongoing remission)
NCT02780583	Treatment of macrophage activation syndrome (mas) with anakinra
NCT02792699	Study to assess if ABP798 is safe & effective in treating moderate to severe rheumatoid arthritis compared to rituximab
NCT02805010	Pharmacokinetics, safety and tolerability study of single dose of abatacept 125mg administered subcutaneously
NCT02819726	A study to compare the pharmacokinetics, pharmacodynamics, safety, and efficacy of sait101 versus Mabthera® versus Rituxan® in patients with rheumatoid arthritis (RA)
NCT02833350	Safety and efficacy study of GDC-0853 compared with placebo and adalimumab in participants with rheumatoid arthritis (RA)
NCT02837146	Ultrasound as imaging biomarker of early response to tocilizumab and methotrexate in very early rheumatoid arthritis
NCT02840175	Treatment tapering in JIA with inactive disease
NCT02843789	Evolution of adipokines and body composition in rheumatoid arthritis patients receiving tocilizumab therapy
NCT02862574	GS-5745 as add-on therapy to a tumor necrosis factor inhibitor and methotrexate regimen in adults with moderately to severely active rheumatoid arthritis
NCT02889796	Filgotinib in combination with methotrexate in adults with moderately to severely active rheumatoid arthritis who have an inadequate response to methotrexate
NCT02908217	Safety and efficacy of tocilizumab versus placebo in polymyalgia rheumatica with glucocorticoid dependence semaphore
NCT02915159	A study to assess the efficacy and safety of abatacept in adults with active primary Sjögren's syndrome
NCT02935387	Remission induction in very early rheumatoid arthritis
NCT02937701	Study to assess if abp710 is safe & effective in treating moderate to severe rheumatoid arthritis compared to infliximab
NCT02986139	Assess the injection site pain associated with a new etanercept formulation in adult subjects with RA or PSA
NCT02990806	A phase 3 study of ni-071 in patients with rheumatoid arthritis (RADIANCE)
NTR1011	Hypothesis generating study to identify the changes in synovial tissue early after initiation of infliximab therapy
NTR1088	Sevra-trial safety and efficacy of vaccination with t cell-dependent and t cell-independent primary and recall antigens in patients with rheumatoid arthritis treated with anti TNF-a antibodies (adalimumab) and anti B cell therapy (rituximab).
NTR1137	An open-label pilot study on the effects of trivalent inactivated influenza vaccination (Influvac®) in rheumatoid arthritis patients treated with rituximab

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NTR1210	Exploratory trial on intra-articular etanercept treatment in inflammatory arthritis
NTR144	Strategies in early arthritis management
NTR1605	(English) Cost-effectiveness of new medicines (Mabthera and Orencia) compared to a second TNF blocking medicine, for patients with inadequate effect of a first TNF blocking medicine. (Dutch) Onderzoek naar de kosteneffectiviteit van nieuwe medicijnen (Mabthera en Orencia) vergeleken met een tweede TNF blokerend middel, voor patienten met onvoldoende effect van een eerste behandeling met TNF blokkerende middelen
NTR2911	Tocilizumab met biopten cohort. Tocilizumab with biopsy cohort
NTR3216	Onderzoek naar non inferioriteit van afbouw en stop behandelstrategieën van adalimumab of etanercept bij patiënten met reumatoïde artritis: kosten besparen tegen welke prijs?
NTR3327	Influence of rituximab on endothelial dysfunction in RA
NTR3509	Therapeutic drug monitoring: toward tailored dosing of adalimumab in rheumatoid arthritis
NTR383	The efficacy and safety of intra-articular injections with the TNF-a antagonist infliximab in patients with chronic or recurrent arthritis of the knee
NTR3903	Dose-to-target of etanercept treatment in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis
NTR5279	The effect of switching treatment from innovator infliximab to infliximab biosimilar on efficacy, safety and immunogenicity in patients with rheumatoid arthritis, spondyloarthritis or psoriatic arthritis in daily clinical care
NTR801	IMPROVED: Induction therapy with methotrexate and prednisone in rheumatoid or very early arthritic disease
NTR851	Prospective study on the effects of rituximab on synovial tissue of patients with rheumatoid arthritis
NTR859	Identification of predictive factors in synovial samples for the clinical response to TNF-alpha blockade in rheumatoid arthritis
SLCTR/2008/008	Efficacy of low dose rituximab with methotrexate compared to leflunomide with methotrexate in patients with refractory rheumatoid arthritis: a randomized double blind controlled clinical trial

Appendix 3. ACR50: main analysis

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
MP + MTX	PL + MTX	1.52 (0.63, 3.70)	1.25 (0.75, 1.76)	0.10 (-0.10, 0.31)
SD ADA SC		0.82 (0.51, 1.33)	0.89 (0.64, 1.17)	-0.05 (-0.15, 0.07)
SD ADA SC + MTX		2.17 (1.70, 2.84)	1.46 (1.31, 1.64)	0.19 (0.13, 0.25)
SD INF IV + MTX		1.88 (1.20, 3.30)	1.38 (1.11, 1.71)	0.16 (0.05, 0.29)

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SD RITUX IV + MTX		1.71 (1.00, 2.95)	1.32 (1.00, 1.64)	0.13 (0.00, 0.26)
SD ABA IV + MTX		1.84 (1.08, 3.14)	1.37 (1.05, 1.68)	0.15 (0.02, 0.28)
SD ETN SC + MTX		2.52 (1.46, 4.38)	1.55 (1.23, 1.85)	0.23 (0.09, 0.34)
SD GOLI SC + MTX		1.61 (0.88, 2.98)	1.29 (0.93, 1.65)	0.12 (-0.03, 0.26)
LD RITUX IV + MTX		1.48 (0.86, 2.54)	1.23 (0.92, 1.56)	0.10 (-0.04, 0.23)
HD GOLI SC		1.17 (0.63, 2.17)	1.09 (0.74, 1.47)	0.04 (-0.11, 0.19)
HD GOLI SC + MTX		1.38 (0.74, 2.55)	1.19 (0.83, 1.56)	0.08 (-0.07, 0.23)
HD INF IV + MTX		2.20 (1.37, 3.81)	1.47 (1.19, 1.78)	0.19 (0.08, 0.32)
SD ADA SC	MP + MTX	0.54 (0.20, 1.47)	0.71 (0.44, 1.27)	-0.15 (-0.38, 0.09)
SD ADA SC + MTX		1.43 (0.57, 3.57)	1.17 (0.82, 1.97)	0.09 (-0.13, 0.31)
SD INF IV + MTX		1.24 (0.60, 2.66)	1.10 (0.83, 1.71)	0.05 (-0.12, 0.23)
SD RITUX IV + MTX		1.12 (0.40, 3.15)	1.06 (0.68, 1.83)	0.03 (-0.22, 0.27)
SD ABA IV + MTX		1.22 (0.43, 3.35)	1.09 (0.71, 1.88)	0.05 (-0.20, 0.29)
SD ETN SC + MTX		1.66 (0.58, 4.64)	1.24 (0.82, 2.11)	0.12 (-0.12, 0.36)
SD GOLI SC + MTX		1.07 (0.36, 3.08)	1.03 (0.64, 1.81)	0.02 (-0.24, 0.27)
LD RITUX IV + MTX		0.97 (0.34, 2.71)	0.99 (0.63, 1.72)	-0.01 (-0.25, 0.24)
HD GOLI SC		0.77 (0.26, 2.21)	0.88 (0.52, 1.57)	-0.06 (-0.32, 0.19)
HD GOLI SC + MTX		0.90 (0.30, 2.64)	0.95 (0.58, 1.69)	-0.02 (-0.28, 0.23)
HD INF IV + MTX		1.46 (0.61, 3.55)	1.18 (0.83, 1.92)	0.09 (-0.11, 0.30)
SD ADA SC + MTX	SD ADA SC	2.65 (1.65, 4.30)	1.65 (1.26, 2.27)	0.24 (0.12, 0.34)
SD INF IV + MTX		2.29 (1.21, 4.80)	1.55 (1.10, 2.30)	0.20 (0.05, 0.37)
SD RITUX IV + MTX		2.08 (1.01, 4.28)	1.48 (1.01, 2.20)	0.18 (0.00, 0.34)
SD ABA IV + MTX		2.25 (1.09, 4.57)	1.54 (1.05, 2.25)	0.20 (0.02, 0.36)
SD ETN SC + MTX		3.08 (1.48, 6.34)	1.74 (1.22, 2.51)	0.27 (0.10, 0.43)
SD GOLI SC + MTX		1.96 (0.91, 4.28)	1.45 (0.95, 2.18)	0.16 (-0.02, 0.34)
LD RITUX IV + MTX		1.80 (0.88, 3.67)	1.39 (0.93, 2.07)	0.14 (-0.03, 0.31)
HD GOLI SC		1.42 (0.65, 3.08)	1.23 (0.77, 1.91)	0.08 (-0.10, 0.27)
HD GOLI SC + MTX		1.68 (0.77, 3.66)	1.34 (0.86, 2.05)	0.13 (-0.06, 0.31)

(Continued)

HD INF IV + MTX		2.69 (1.37, 5.55)	1.66 (1.17, 2.42)	0.24 (0.08, 0.40)
SD INF IV + MTX	SD ADA SC + MTX	0.87 (0.52, 1.58)	0.94 (0.74, 1.18)	-0.03 (-0.16, 0.11)
SD RITUX IV + MTX		0.79 (0.43, 1.42)	0.90 (0.67, 1.14)	-0.06 (-0.21, 0.08)
SD ABA IV + MTX		0.85 (0.46, 1.52)	0.93 (0.70, 1.17)	-0.04 (-0.19, 0.10)
SD ETN SC + MTX		1.16 (0.63, 2.11)	1.06 (0.82, 1.28)	0.04 (-0.11, 0.16)
SD GOLI SC + MTX		0.74 (0.38, 1.43)	0.88 (0.62, 1.14)	-0.07 (-0.24, 0.08)
LD RITUX IV + MTX		0.68 (0.37, 1.22)	0.84 (0.61, 1.08)	-0.09 (-0.24, 0.05)
HD GOLI SC		0.54 (0.27, 1.04)	0.75 (0.50, 1.02)	-0.15 (-0.31, 0.01)
HD GOLI SC + MTX		0.63 (0.32, 1.23)	0.82 (0.56, 1.08)	-0.11 (-0.27, 0.05)
HD INF IV + MTX		1.02 (0.58, 1.82)	1.01 (0.79, 1.24)	0.00 (-0.13, 0.14)
SD RITUX IV + MTX	SD INF IV + MTX	0.91 (0.41, 1.81)	0.96 (0.67, 1.29)	-0.02 (-0.21, 0.14)
SD ABA IV + MTX		0.98 (0.45, 1.93)	0.99 (0.70, 1.32)	-0.01 (-0.19, 0.16)
SD ETN SC + MTX		1.34 (0.60, 2.68)	1.12 (0.82, 1.47)	0.07 (-0.12, 0.23)
SD GOLI SC + MTX		0.86 (0.37, 1.79)	0.94 (0.63, 1.28)	-0.04 (-0.24, 0.14)
LD RITUX IV + MTX		0.79 (0.36, 1.55)	0.90 (0.62, 1.22)	-0.06 (-0.25, 0.11)
HD GOLI SC		0.62 (0.27, 1.30)	0.79 (0.51, 1.13)	-0.12 (-0.31, 0.07)
HD GOLI SC + MTX		0.73 (0.32, 1.53)	0.87 (0.57, 1.21)	-0.08 (-0.28, 0.10)
HD INF IV + MTX		1.17 (0.69, 1.87)	1.07 (0.86, 1.29)	0.04 (-0.09, 0.15)
SD ABA IV + MTX	SD RITUX IV + MTX	1.08 (0.50, 2.29)	1.03 (0.73, 1.46)	0.02 (-0.17, 0.20)
SD ETN SC + MTX		1.48 (0.68, 3.18)	1.17 (0.86, 1.62)	0.09 (-0.09, 0.27)
SD GOLI SC + MTX		0.94 (0.42, 2.13)	0.97 (0.66, 1.41)	-0.01 (-0.21, 0.18)
LD RITUX IV + MTX		0.86 (0.50, 1.50)	0.93 (0.72, 1.21)	-0.04 (-0.17, 0.10)
HD GOLI SC		0.68 (0.30, 1.55)	0.83 (0.53, 1.24)	-0.10 (-0.29, 0.11)
HD GOLI SC + MTX		0.81 (0.36, 1.83)	0.90 (0.60, 1.33)	-0.05 (-0.25, 0.15)
HD INF IV + MTX		1.29 (0.63, 2.82)	1.11 (0.83, 1.57)	0.06 (-0.11, 0.25)
SD ETN SC + MTX	SD ABA IV + MTX	1.37 (0.64, 2.94)	1.13 (0.84, 1.55)	0.07 (-0.10, 0.25)
SD GOLI SC + MTX		0.88 (0.39, 1.98)	0.94 (0.64, 1.35)	-0.03 (-0.23, 0.16)
LD RITUX IV + MTX		0.80 (0.38, 1.72)	0.90 (0.63, 1.28)	-0.05 (-0.24, 0.13)

(Continued)

HD GOLI SC		0.63 (0.28, 1.44)	0.80 (0.52, 1.19)	-0.11 (-0.30, 0.09)
HD GOLI SC + MTX		0.75 (0.33, 1.68)	0.87 (0.58, 1.27)	-0.07 (-0.26, 0.13)
HD INF IV + MTX		1.20 (0.59, 2.58)	1.08 (0.81, 1.49)	0.04 (-0.13, 0.22)
SD GOLI SC + MTX	SD ETN SC + MTX	0.64 (0.28, 1.45)	0.83 (0.58, 1.16)	-0.11 (-0.30, 0.09)
LD RITUX IV + MTX		0.59 (0.27, 1.26)	0.80 (0.57, 1.10)	-0.13 (-0.30, 0.06)
HD GOLI SC		0.46 (0.20, 1.06)	0.71 (0.47, 1.02)	-0.19 (-0.37, 0.01)
HD GOLI SC + MTX		0.55 (0.24, 1.24)	0.77 (0.52, 1.09)	-0.15 (-0.34, 0.05)
HD INF IV + MTX		0.87 (0.42, 1.92)	0.95 (0.73, 1.28)	-0.03 (-0.20, 0.15)
LD RITUX IV + MTX	SD GOLI SC + MTX	0.92 (0.40, 2.06)	0.96 (0.65, 1.43)	-0.02 (-0.22, 0.18)
HD GOLI SC		0.72 (0.39, 1.33)	0.85 (0.61, 1.16)	-0.08 (-0.22, 0.07)
HD GOLI SC + MTX		0.85 (0.47, 1.57)	0.93 (0.68, 1.25)	-0.04 (-0.18, 0.11)
HD INF IV + MTX		1.37 (0.63, 3.10)	1.14 (0.83, 1.67)	0.08 (-0.11, 0.27)
HD GOLI SC	LD RITUX IV + MTX	0.79 (0.35, 1.79)	0.88 (0.57, 1.34)	-0.06 (-0.25, 0.14)
HD GOLI SC + MTX		0.93 (0.41, 2.10)	0.97 (0.63, 1.44)	-0.02 (-0.22, 0.18)
HD INF IV + MTX		1.49 (0.73, 3.23)	1.19 (0.88, 1.70)	0.10 (-0.07, 0.28)
HD GOLI SC + MTX	HD GOLI SC	1.18 (0.64, 2.19)	1.09 (0.79, 1.53)	0.04 (-0.11, 0.19)
HD INF IV + MTX		1.89 (0.87, 4.37)	1.35 (0.94, 2.08)	0.16 (-0.03, 0.35)
HD INF IV + MTX	HD GOLI SC + MTX	1.60 (0.74, 3.66)	1.23 (0.88, 1.85)	0.12 (-0.07, 0.31)

Random-effects model	Residual deviance	34.01 vs 33 data-points
	Deviance information criteria	233.176
Fixed-effect model	Residual deviance	34.92 vs 33 data-points
	Deviance information criteria	232.343

ABA: abatacept

ADA: adalimumab

CrI: credible interval

(Continued)

ETN: etanercept

GOLI: golimumab

HD: high dose

INF: infliximab

IV: intravenous

LD: low dose

MP: methylprednisolone

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RITUX: rituximab

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 4. Subgroup analysis: ACR50, established RA

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC	PL + MTX	0.80 (0.46, 1.43)	0.87 (0.59, 1.22)	-0.05 (-0.16, 0.09)
SD ADA SC + MTX		2.07 (1.51, 3.02)	1.46 (1.25, 1.71)	0.18 (0.10, 0.27)
SD ABA IV + MTX		1.85 (1.00, 3.43)	1.39 (1.00, 1.77)	0.15 (0.00, 0.30)
SD ETN SC + MTX		2.52 (1.37, 4.70)	1.58 (1.19, 1.94)	0.23 (0.08, 0.36)
SD GOLI SC + MTX		1.63 (0.82, 3.25)	1.31 (0.88, 1.74)	0.12 (-0.05, 0.28)
HD GOLI SC		1.17 (0.59, 2.36)	1.10 (0.70, 1.55)	0.04 (-0.12, 0.21)
HD GOLI SC + MTX		1.38 (0.70, 2.76)	1.20 (0.79, 1.65)	0.08 (-0.08, 0.25)
SD ADA SC + MTX	SD ADA SC	2.58 (1.51, 4.60)	1.67 (1.22, 2.45)	0.23 (0.10, 0.35)
SD ABA IV + MTX		2.30 (1.00, 5.24)	1.58 (1.00, 2.51)	0.20 (0.00, 0.38)
SD ETN SC + MTX		3.13 (1.36, 7.20)	1.80 (1.17, 2.79)	0.28 (0.07, 0.45)
SD GOLI SC + MTX		2.03 (0.83, 4.85)	1.50 (0.90, 2.41)	0.17 (-0.04, 0.37)
HD GOLI SC		1.46 (0.60, 3.53)	1.26 (0.72, 2.11)	0.09 (-0.12, 0.29)

(Continued)

HD GOLI SC + MTX		1.72 (0.71, 4.16)	1.38 (0.81, 2.28)	0.13 (-0.08, 0.33)
SD ABA IV + MTX	SD ADA SC + MTX	0.89 (0.43, 1.76)	0.95 (0.66, 1.25)	-0.03 (-0.21, 0.13)
SD ETN SC + MTX		1.22 (0.59, 2.40)	1.08 (0.79, 1.37)	0.05 (-0.13, 0.20)
SD GOLI SC + MTX		0.79 (0.36, 1.65)	0.90 (0.59, 1.22)	-0.06 (-0.25, 0.12)
HD GOLI SC		0.56 (0.26, 1.20)	0.75 (0.47, 1.08)	-0.14 (-0.32, 0.05)
HD GOLI SC + MTX		0.67 (0.30, 1.41)	0.82 (0.53, 1.15)	-0.10 (-0.29, 0.08)
SD ETN SC + MTX	SD ABA IV + MTX	1.36 (0.57, 3.27)	1.14 (0.79, 1.65)	0.07 (-0.13, 0.28)
SD GOLI SC + MTX		0.88 (0.35, 2.22)	0.94 (0.60, 1.45)	-0.03 (-0.25, 0.19)
HD GOLI SC		0.63 (0.25, 1.60)	0.79 (0.48, 1.26)	-0.11 (-0.32, 0.11)
HD GOLI SC + MTX		0.75 (0.30, 1.89)	0.87 (0.54, 1.35)	-0.07 (-0.29, 0.15)
SD GOLI SC + MTX	SD ETN SC + MTX	0.65 (0.26, 1.62)	0.83 (0.54, 1.23)	-0.11 (-0.32, 0.11)
HD GOLI SC		0.46 (0.19, 1.18)	0.70 (0.43, 1.08)	-0.19 (-0.39, 0.04)
HD GOLI SC + MTX		0.55 (0.22, 1.39)	0.76 (0.48, 1.15)	-0.15 (-0.35, 0.08)
HD GOLI SC	SD GOLI SC + MTX	0.72 (0.36, 1.42)	0.84 (0.58, 1.20)	-0.08 (-0.24, 0.08)
HD GOLI SC + MTX		0.85 (0.43, 1.66)	0.92 (0.65, 1.29)	-0.04 (-0.20, 0.12)
HD GOLI SC + MTX	HD GOLI SC	1.18 (0.60, 2.32)	1.09 (0.76, 1.60)	0.04 (-0.12, 0.2)

Random-effects model	Residual deviance	17.84 vs 17 data-points
	Deviance information criteria	126.687
Fixed-effect model	Residual deviance	18.05 vs 17 data-points
	Deviance information criteria	125.82

ABA: abatacept

ADA: adalimumab

CrI: credible interval

ETN: etanercept

GOLI: golimumab

HD: high dose

(Continued)

INF: infliximab

IV: intravenous

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RITUX: rituximab

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 5. Subgroup analysis 2: ACR50, trial duration ≤ 6 months

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC + MTX	PL + MTX	2.41 (1.74, 3.66)	1.59 (1.35, 1.91)	0.22 (0.14, 0.31)
SD GOLI SC + MTX		1.64 (0.80, 3.29)	1.33 (0.87, 1.82)	0.12 (-0.05, 0.29)
HD GOLI SC		1.18 (0.58, 2.38)	1.11 (0.69, 1.60)	0.04 (-0.12, 0.21)
HD GOLI SC + MTX		1.40 (0.69, 2.80)	1.22 (0.78, 1.71)	0.08 (-0.08, 0.25)
SD GOLI SC + MTX	SD ADA SC + MTX	0.68 (0.29, 1.44)	0.84 (0.53, 1.16)	-0.10 (-0.30, 0.09)
HD GOLI SC		0.49 (0.21, 1.03)	0.70 (0.41, 1.01)	-0.18 (-0.36, 0.01)
HD GOLI SC + MTX		0.58 (0.25, 1.22)	0.77 (0.47, 1.09)	-0.13 (-0.33, 0.05)
HD GOLI SC	SD GOLI SC + MTX	0.72 (0.36, 1.44)	0.84 (0.56, 1.22)	-0.08 (-0.24, 0.09)
HD GOLI SC + MTX		0.85 (0.43, 1.70)	0.92 (0.63, 1.33)	-0.04 (-0.20, 0.13)
HD GOLI SC + MTX	HD GOLI SC	1.18 (0.59, 2.38)	1.10 (0.74, 1.66)	0.04 (-0.12, 0.20)

Random-effects model	Residual deviance	12.3 vs 12 data-points
	Deviance information criteria	85.785
Fixed-effect model	Residual deviance	13.04 vs 12 data-points
	Deviance information criteria	85.321

(Continued)

ADA: adalimumab

CrI: credible interval

GOLI: golimumab

HD: high dose

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 6. Subgroup analysis 2: ACR50, trial duration 6-12 months

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
MP + MTX	PL + MTX	0.71 (0.11, 5.35)	0.81 (0.18, 1.91)	-0.08 (-0.36, 0.37)
SD INF IV + MTX		1.94 (1.03, 5.77)	1.38 (1.02, 1.98)	0.16 (0.01, 0.39)
SD ABA IV + MTX		1.84 (0.71, 4.79)	1.35 (0.81, 1.86)	0.15 (-0.08, 0.36)
SD ETN SC + MTX		2.52 (0.98, 6.54)	1.51 (0.99, 1.99)	0.22 (-0.01, 0.40)
HD INF IV + MTX		2.24 (1.00, 6.38)	1.45 (1.00, 2.00)	0.20 (0.00, 0.40)
SD INF IV + MTX	MP + MTX	2.82 (0.49, 17.20)	1.70 (0.81, 7.32)	0.25 (-0.14, 0.53)
SD ABA IV + MTX		2.63 (0.28, 20.99)	1.65 (0.62, 7.72)	0.23 (-0.27, 0.57)
SD ETN SC + MTX		3.60 (0.38, 28.45)	1.86 (0.73, 8.62)	0.30 (-0.19, 0.63)
HD INF IV + MTX		3.21 (0.44, 22.82)	1.79 (0.78, 8.04)	0.27 (-0.16, 0.59)
SD ABA IV + MTX	SD INF IV + MTX	0.95 (0.21, 2.75)	0.98 (0.51, 1.45)	-0.01 (-0.34, 0.22)
SD ETN SC + MTX		1.30 (0.28, 3.76)	1.10 (0.62, 1.58)	0.06 (-0.27, 0.28)
HD INF IV + MTX		1.16 (0.41, 2.57)	1.06 (0.71, 1.39)	0.03 (-0.19, 0.20)
SD ETN SC + MTX	SD ABA IV + MTX	1.37 (0.35, 5.21)	1.12 (0.67, 1.95)	0.07 (-0.23, 0.35)
HD INF IV + MTX		1.21 (0.36, 5.03)	1.08 (0.68, 1.94)	0.05 (-0.22, 0.35)
HD INF IV + MTX	SD ETN SC + MTX	0.89 (0.26, 3.77)	0.96 (0.62, 1.62)	-0.03 (-0.28, 0.28)

(Continued)

Random-effects model	Residual deviance	11.35 vs 11 data-points
	Deviance information criteria	75.5
Fixed-effect model	Residual deviance	11.62 vs 11 data-points
	Deviance information criteria	75.511

ABA: abatacept

CrI: credible interval

ETN: etanercept

HD: high dose

INF: infliximab

IV: intravenous

MP: methylprednisolone

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 7. Subgroup analysis 2: ACR50, trial duration > 12 months

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC	PL + MTX	0.74 (0.37, 1.44)	0.84 (0.53, 1.20)	-0.07 (-0.22, 0.09)
SD ADA SC + MTX		1.78 (1.01, 3.03)	1.31 (1.00, 1.60)	0.14 (0.00, 0.26)
SD RITUX IV + MTX		1.71 (0.84, 3.53)	1.29 (0.91, 1.65)	0.13 (-0.04, 0.29)
LD RITUX IV + MTX		1.48 (0.72, 3.06)	1.21 (0.83, 1.58)	0.10 (-0.08, 0.26)
SD ADA SC + MTX	SD ADA SC	2.40 (1.20, 4.66)	1.55 (1.09, 2.34)	0.21 (0.04, 0.36)
SD RITUX IV + MTX		2.30 (0.88, 6.30)	1.53 (0.94, 2.56)	0.20 (-0.03, 0.42)

(Continued)

LD RITUX IV + MTX		1.99 (0.76, 5.43)	1.44 (0.87, 2.43)	0.17 (-0.06, 0.39)
SD RITUX IV + MTX	SD ADA SC + MTX	0.96 (0.40, 2.44)	0.98 (0.67, 1.40)	-0.01 (-0.22, 0.20)
LD RITUX IV + MTX		0.83 (0.35, 2.12)	0.93 (0.62, 1.34)	-0.04 (-0.25, 0.17)
LD RITUX IV + MTX	SD RITUX IV + MTX	0.86 (0.42, 1.79)	0.94 (0.69, 1.28)	-0.04 (-0.20, 0.13)

Random-effects model	Residual deviance	7.554 vs 8 data-points
	Deviance information criteria	60.272
Fixed-effect model	Residual deviance	7.305 vs 8 data-points
	Deviance information criteria	59.607

ADA: adalimumab

CrI: credible interval

IV: intravenous

LD: low dose

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RITUX: rituximab

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 8. HAQ: main analysis

Treatment	Reference	MD (95% CrI)
MP + MTX	MTX	-0.17 (-0.63, 0.27)
SD ADA SC		0.00 (-0.42, 0.42)
SD ETN SC		0.40 (-0.33, 1.14)

(Continued)

SD INF IV + MTX		-0.03 (-0.37, 0.25)
SD ADA SC + MTX		-0.30 (-0.59, -0.02)
SD ETN SC + MTX		-0.10 (-0.43, 0.24)
SD ABA IV + MTX		-0.20 (-0.65, 0.25)
SD RITUX IV + MTX		-0.24 (-0.68, 0.21)
LD RITUX IV + MTX		-0.24 (-0.69, 0.21)
HD INF IV + MTX		0.12 (-0.32, 0.54)
SD ADA SC	MP + MTX	0.17 (-0.43, 0.80)
SD ETN SC		0.57 (-0.28, 1.45)
SD INF IV + MTX		0.14 (-0.21, 0.45)
SD ADA SC + MTX		-0.13 (-0.65, 0.41)
SD ETN SC + MTX		0.07 (-0.46, 0.65)
SD ABA IV + MTX		-0.03 (-0.64, 0.63)
SD RITUX IV + MTX		-0.07 (-0.68, 0.58)
LD RITUX IV + MTX		-0.07 (-0.67, 0.59)
HD INF IV + MTX		0.29 (-0.24, 0.83)
SD ETN SC	SD ADA SC	0.41 (-0.44, 1.25)
SD INF IV + MTX		-0.03 (-0.58, 0.46)
SD ADA SC + MTX		-0.30 (-0.72, 0.12)
SD ETN SC + MTX		-0.10 (-0.63, 0.44)
SD ABA IV + MTX		-0.20 (-0.81, 0.41)
SD RITUX IV + MTX		-0.24 (-0.84, 0.37)
LD RITUX IV + MTX		-0.24 (-0.85, 0.38)
HD INF IV + MTX		0.12 (-0.50, 0.70)
SD INF IV + MTX	SD ETN SC	-0.44 (-1.25, 0.35)
SD ADA SC + MTX		-0.71 (-1.50, 0.09)
SD ETN SC + MTX		-0.50 (-1.31, 0.33)
SD ABA IV + MTX		-0.60 (-1.46, 0.26)

(Continued)

SD RITUX IV + MTX		-0.64 (-1.49, 0.22)
LD RITUX IV + MTX		-0.64 (-1.50, 0.22)
HD INF IV + MTX		-0.28 (-1.14, 0.56)
SD ADA SC + MTX	SD INF IV + MTX	-0.27 (-0.66, 0.17)
SD ETN SC + MTX		-0.07 (-0.49, 0.42)
SD ABA IV + MTX		-0.17 (-0.67, 0.41)
SD RITUX IV + MTX		-0.21 (-0.72, 0.37)
LD RITUX IV + MTX		-0.21 (-0.71, 0.36)
HD INF IV + MTX		0.15 (-0.25, 0.60)
SD ETN SC + MTX	SD ADA SC + MTX	0.21 (-0.23, 0.65)
SD ABA IV + MTX		0.10 (-0.43, 0.63)
SD RITUX IV + MTX		0.06 (-0.47, 0.59)
LD RITUX IV + MTX		0.06 (-0.46, 0.59)
HD INF IV + MTX		0.43 (-0.10, 0.93)
SD ABA IV + MTX	SD ETN SC + MTX	-0.10 (-0.67, 0.46)
SD RITUX IV + MTX		-0.14 (-0.70, 0.42)
LD RITUX IV + MTX		-0.14 (-0.70, 0.41)
HD INF IV + MTX		0.22 (-0.33, 0.75)
SD RITUX IV + MTX	SD ABA IV + MTX	-0.04 (-0.67, 0.60)
LD RITUX IV + MTX		-0.04 (-0.67, 0.59)
HD INF IV + MTX		0.32 (-0.32, 0.91)
LD RITUX IV + MTX	SD RITUX IV + MTX	0.00 (-0.44, 0.45)
HD INF IV + MTX		0.36 (-0.26, 0.96)
HD INF IV + MTX	LD RITUX IV + MTX	0.36 (-0.27, 0.96)

Random-effects model	Total Residual deviance	30.22 vs 31 data-points
	Deviance information criteria	-69.557
Fixed-effect model	Total Residual deviance	43.38 vs 31 data-points

(Continued)

	Deviance information criteria	-60.97

ABA: abatacept

ADA: adalimumab

CrI: credible interval

ETN: etanercept

HD: high dose

INF: infliximab

IV: intravenous

LD: low dose

MD: mean difference

MP: methylprednisolone

MTX: methotrexate

RITUX: rituximab

SC: subcutaneous

SD: standard dose

Appendix 9. Subgroup analysis: HAQ, early RA

Treatment	Reference	MD (95% CrI)
MP + MTX	MTX + PL	-0.04 (-1.58, 1.51)
SD INF IV + MTX		0.09 (-1.01, 1.17)
SD ETN SC + MTX		-0.09 (-1.62, 1.46)
SD RITUX IV + MTX		-0.24 (-1.75, 1.28)
LD RITUX IV + MTX		-0.24 (-1.77, 1.29)
HD INF IV + MTX		0.19 (-1.26, 1.61)
SD INF IV + MTX	MP + MTX	0.13 (-0.98, 1.20)
SD ETN SC + MTX		-0.05 (-2.23, 2.14)
SD RITUX IV + MTX		-0.20 (-2.37, 1.97)
LD RITUX IV + MTX		-0.20 (-2.35, 1.98)
HD INF IV + MTX		0.23 (-1.58, 2.01)

(Continued)

SD ETN SC + MTX	SD INF IV + MTX	-0.18 (-2.04, 1.72)
SD RITUX IV + MTX		-0.33 (-2.17, 1.55)
LD RITUX IV + MTX		-0.33 (-2.18, 1.57)
HD INF IV + MTX		0.10 (-1.33, 1.54)
SD RITUX IV + MTX	SD ETN SC + MTX	-0.15 (-2.32, 2.01)
LD RITUX IV + MTX		-0.15 (-2.32, 2.02)
HD INF IV + MTX		0.28 (-1.83, 2.37)
LD RITUX IV + MTX	SD RITUX IV + MTX	0.00 (-1.51, 1.53)
HD INF IV + MTX		0.43 (-1.64, 2.49)
HD INF IV + MTX	LD RITUX IV + MTX	0.43 (-1.66, 2.50)

Random-effects model	Residual deviance	13.9 vs 14 data-points
	Deviance information criteria	-39.969
Fixed-effect model	Residual deviance	25.44 vs 14 data-points
	Deviance information criteria	-30.231
Note:		

Total participants	2068
Total studies	6
2-arm	4
3-arm	2

CrI: credible interval

ETN: etanercept

HD: high dose

INF: infliximab

IV: intravenous

LD: low dose

MD: mean difference

MP: methylprednisolone

(Continued)

MTX: methotrexate

PL: placebo

RITUX: rituximab

SC: subcutaneous

SD: standard dose

Appendix 10. Subgroup analysis: HAQ, established RA

Treatment	Reference	MD (95% CrI)
SD ADA SC	MTX + PL	0.00 (-0.48, 0.48)
SD ADA SC + MTX		-0.30 (-0.61, 0.01)
SD INF IV + MTX		-0.31 (-0.87, 0.19)
SD ETN SC + MTX		-0.10 (-0.61, 0.43)
SD ABA IV + MTX		-0.20 (-0.70, 0.31)
SD ADA SC + MTX	SD ADA SC	-0.30 (-0.78, 0.17)
SD INF IV + MTX		-0.31 (-1.04, 0.35)
SD ETN SC + MTX		-0.10 (-0.80, 0.62)
SD ABA IV + MTX		-0.20 (-0.89, 0.50)
SD INF IV + MTX	SD ADA SC + MTX	-0.01 (-0.65, 0.56)
SD ETN SC + MTX		0.20 (-0.40, 0.81)
SD ABA IV + MTX		0.10 (-0.48, 0.69)
SD ETN SC + MTX	SD INF IV + MTX	0.21 (-0.49, 0.99)
SD ABA IV + MTX		0.11 (-0.57, 0.87)
SD ABA IV + MTX	SD ETN SC + MTX	-0.10 (-0.83, 0.63)

Random-effects model	Residual deviance	13.06 vs 15 data-points
	Deviance information criteria	-31.935
Fixed-effect model	Residual deviance	12.09 vs 15 data-points

(Continued)

	Deviance information criteria	-33.894

Note:

Total participants	2078
Total studies	7
2-arm	6
3-arm	1

ABA: abatacept

ADA: adalimumab

CrI: credible interval

ETN: etanercept

INF: infliximab

IV: intravenous

MD: mean difference

MTX: methotrexate

PL: placebo

SC: subcutaneous

SD: standard dose

Appendix 11. Subgroup analysis 2: HAQ, trial duration ≤ 6 months

Treatment	Reference	MD (95% CrI)
MP + MTX	MTX + PL	-0.22 (-3.80, 3.33)
SD ETN SC		0.40 (-2.17, 2.97)
SD INF IV + MTX		-0.31 (-2.82, 2.19)
SD ADA SC + MTX		-0.31 (-2.84, 2.22)
SD ETN SC	MP + MTX	0.62 (-3.76, 5.05)
SD INF IV + MTX		-0.09 (-2.60, 2.45)
SD ADA SC + MTX		-0.10 (-4.44, 4.28)
SD INF IV + MTX	SD ETN SC	-0.71 (-4.31, 2.89)

(Continued)

SD ADA SC + MTX		-0.71 (-4.31, 2.91)
SD ADA SC + MTX	SD INF IV + MTX	0.00 (-3.56, 3.63)

Random-effects model	Residual deviance	8.01 vs 8 data-points
	Deviance information criteria	-3.373
Fixed-effect model	Residual deviance	8.012 vs 8 data-points
	Deviance information criteria	-3.369
Note:		

Total participants	243
Total studies	4
2-arm	4

ADA: adalimumab

CrI: credible interval

ETN: etanercept

INF: infliximab

IV: intravenous

MD: mean difference

MP: methylprednisolone

MTX: methotrexate

PL: placebo

SC: subcutaneous

SD: standard dose

Appendix 12. Subgroup analysis 2: HAQ, trial duration 6-12 months

Treatment	Reference	MD (95% CrI)
MP + MTX	MTX + PL	-0.21 (-1.28, 0.78)
SD INF IV + MTX		0.11 (-0.54, 0.69)
SD ETN SC + MTX		-0.10 (-0.68, 0.48)

(Continued)

SD ABA IV + MTX		-0.20 (-1.03, 0.62)
HD INF IV + MTX		0.20 (-0.60, 0.94)
SD INF IV + MTX	MP + MTX	0.32 (-0.49, 1.16)
SD ETN SC + MTX		0.11 (-1.05, 1.36)
SD ABA IV + MTX		0.01 (-1.27, 1.36)
HD INF IV + MTX		0.40 (-0.71, 1.55)
SD ETN SC + MTX	SD INF IV + MTX	-0.21 (-1.03, 0.69)
SD ABA IV + MTX		-0.31 (-1.31, 0.75)
HD INF IV + MTX		0.08 (-0.68, 0.86)
SD ABA IV + MTX	SD ETN SC + MTX	-0.10 (-1.12, 0.91)
HD INF IV + MTX		0.29 (-0.70, 1.23)
HD INF IV + MTX	SD ABA IV + MTX	0.40 (-0.77, 1.50)

Random-effects model	Residual deviance	12.03 vs 13 data-points
	Deviance information criteria	-40.422
Fixed-effect model	Residual deviance	11.12 vs 13 data-points
	Deviance information criteria	-42.312
Note:		

Total participants	2214
Total studies	6
2-arm	5
3-arm	1

ABA: abatacept

CrI: credible interval

ETN: etanercept

HD: high dose

INF: infliximab

(Continued)

IV: intravenous

MD: mean difference

MP: methylprednisolone

MTX: methotrexate

PL: placebo

SC: subcutaneous

SD: standard dose

Appendix 13. Subgroup analysis 2: HAQ, trial duration > 12 months

Treatment	Reference	MD (95% CrI)
SD ADA SC	MTX + PL	0.00 (-1.58, 1.56)
SD ADA SC + MTX		-0.30 (-1.50, 0.88)
SD INF IV + MTX		-0.52 (-2.63, 1.58)
SD RITUX IV + MTX		-0.24 (-1.93, 1.45)
LD RITUX IV + MTX		-0.24 (-1.89, 1.42)
SD ADA SC + MTX	SD ADA SC	-0.30 (-1.88, 1.28)
SD INF IV + MTX		-0.52 (-3.07, 2.07)
SD RITUX IV + MTX		-0.24 (-2.53, 2.08)
LD RITUX IV + MTX		-0.24 (-2.51, 2.06)
SD INF IV + MTX	SD ADA SC + MTX	-0.22 (-2.60, 2.18)
SD RITUX IV + MTX		0.06 (-1.99, 2.15)
LD RITUX IV + MTX		0.06 (-1.98, 2.11)
SD RITUX IV + MTX	SD INF IV + MTX	0.28 (-2.40, 2.93)
LD RITUX IV + MTX		0.28 (-2.36, 2.92)
LD RITUX IV + MTX	SD RITUX IV + MTX	0.00 (-1.67, 1.68)

Random-effects model	Residual deviance	9.734 vs 10 data-points
	Deviance information criteria	-25.052

(Continued)

Fixed-effect model	Residual deviance	9.012 vs 10 data-points
	Deviance information criteria	-26.494
Note:		
Total participants	1715	
Total studies	4	
2-arm	2	
3-arm	2	

ADA: adalimumab

CrI: credible interval

INF: infliximab

IV: intravenous

LD: low dose

MD: mean difference

MTX: methotrexate

PL: placebo

RITUX: rituximab

SC: subcutaneous

SD: standard dose

Appendix 14. Remission: main analysis

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
MP + MTX	MTX	1.90 (0.75, 5.06)	1.54 (0.80, 2.52)	0.14 (-0.05, 0.38)
SD ADA SC		0.95 (0.51, 1.78)	0.96 (0.58, 1.49)	-0.01 (-0.11, 0.12)
SD INF IV + MTX		1.82 (1.13, 3.49)	1.50 (1.09, 2.18)	0.13 (0.02, 0.29)
SD ADA SC + MTX		2.55 (1.74, 3.76)	1.81 (1.45, 2.24)	0.21 (0.12, 0.31)
SD ABA IV + MTX		2.33 (1.18, 4.64)	1.73 (1.13, 2.42)	0.19 (0.03, 0.36)
SD ADA + MTX		2.26 (0.98, 5.26)	1.70 (0.99, 2.54)	0.18 (0.00, 0.39)
SD ETN SC + MTX		1.39 (0.54, 3.62)	1.26 (0.61, 2.18)	0.07 (-0.10, 0.30)

(Continued)

SD GOLI SC + MTX		2.69 (1.18, 6.23)	1.87 (1.13, 2.70)	0.23 (0.03, 0.43)
SD RITUX IV + MTX		3.22 (1.56, 6.70)	2.04 (1.36, 2.77)	0.27 (0.09, 0.44)
LD RITUX IV + MTX		3.55 (1.72, 7.32)	2.13 (1.45, 2.84)	0.29 (0.12, 0.46)
HD GOLI SC		1.49 (0.63, 3.50)	1.32 (0.70, 2.15)	0.08 (-0.08, 0.29)
HD GOLI SC + MTX		1.93 (0.84, 4.49)	1.55 (0.87, 2.40)	0.14 (-0.03, 0.35)
HD INF IV + MTX		2.80 (1.55, 5.70)	1.91 (1.35, 2.64)	0.24 (0.09, 0.40)
SD ADA SC	MP + MTX	0.50 (0.16, 1.53)	0.62 (0.31, 1.36)	-0.15 (-0.40, 0.08)
SD INF IV + MTX		0.96 (0.45, 2.28)	0.98 (0.66, 1.76)	-0.01 (-0.20, 0.17)
SD ADA SC + MTX		1.34 (0.47, 3.73)	1.18 (0.70, 2.34)	0.07 (-0.18, 0.29)
SD ABA IV + MTX		1.23 (0.37, 3.89)	1.12 (0.59, 2.31)	0.05 (-0.23, 0.31)
SD ADA + MTX		1.19 (0.32, 4.16)	1.11 (0.53, 2.35)	0.04 (-0.27, 0.32)
SD ETN SC + MTX		0.73 (0.18, 2.81)	0.82 (0.34, 1.92)	-0.07 (-0.37, 0.23)
SD GOLI SC + MTX		1.42 (0.39, 4.89)	1.21 (0.61, 2.52)	0.08 (-0.22, 0.36)
SD RITUX IV + MTX		1.70 (0.49, 5.58)	1.32 (0.71, 2.70)	0.13 (-0.17, 0.39)
LD RITUX IV + MTX		1.88 (0.55, 6.10)	1.39 (0.75, 2.80)	0.15 (-0.15, 0.41)
HD GOLI SC		0.78 (0.21, 2.73)	0.86 (0.38, 1.90)	-0.06 (-0.34, 0.22)
HD GOLI SC + MTX		1.02 (0.28, 3.57)	1.01 (0.48, 2.18)	0.00 (-0.29, 0.29)
HD INF IV + MTX		1.47 (0.55, 4.17)	1.24 (0.75, 2.39)	0.09 (-0.14, 0.32)
SD INF IV + MTX	SD ADA SC	1.91 (0.92, 4.93)	1.56 (0.95, 3.01)	0.14 (-0.02, 0.33)
SD ADA SC + MTX		2.69 (1.44, 5.02)	1.89 (1.24, 3.06)	0.22 (0.09, 0.33)
SD ABA IV + MTX		2.47 (0.97, 6.19)	1.80 (0.98, 3.27)	0.20 (-0.01, 0.39)
SD ADA + MTX		2.39 (0.84, 6.85)	1.77 (0.89, 3.37)	0.19 (-0.04, 0.42)
SD ETN SC + MTX		1.47 (0.47, 4.63)	1.31 (0.57, 2.77)	0.08 (-0.14, 0.33)
SD GOLI SC + MTX		2.85 (1.01, 8.07)	1.94 (1.01, 3.62)	0.23 (0.00, 0.46)
SD RITUX IV + MTX		3.40 (1.31, 8.94)	2.12 (1.18, 3.81)	0.28 (0.06, 0.48)
LD RITUX IV + MTX		3.75 (1.43, 9.77)	2.21 (1.25, 3.94)	0.30 (0.08, 0.50)
HD GOLI SC		1.57 (0.54, 4.52)	1.37 (0.64, 2.76)	0.09 (-0.12, 0.32)
HD GOLI SC + MTX		2.03 (0.72, 5.81)	1.61 (0.79, 3.13)	0.15 (-0.06, 0.38)

(Continued)

HD INF IV + MTX		2.96 (1.27, 7.72)	1.98 (1.16, 3.65)	0.24 (0.05, 0.44)
SD ADA SC + MTX	SD INF IV + MTX	1.40 (0.64, 2.52)	1.21 (0.79, 1.72)	0.08 (-0.11, 0.22)
SD ABA IV + MTX		1.29 (0.48, 2.82)	1.16 (0.64, 1.76)	0.06 (-0.17, 0.25)
SD ADA + MTX		1.24 (0.42, 3.18)	1.13 (0.58, 1.84)	0.05 (-0.20, 0.28)
SD ETN SC + MTX		0.76 (0.23, 2.15)	0.84 (0.36, 1.54)	-0.06 (-0.30, 0.18)
SD GOLI SC + MTX		1.48 (0.50, 3.75)	1.24 (0.66, 1.96)	0.09 (-0.16, 0.32)
SD RITUX IV + MTX		1.78 (0.64, 4.01)	1.36 (0.78, 2.03)	0.14 (-0.11, 0.33)
LD RITUX IV + MTX		1.96 (0.70, 4.43)	1.42 (0.82, 2.10)	0.17 (-0.09, 0.35)
HD GOLI SC		0.81 (0.27, 2.10)	0.88 (0.41, 1.53)	-0.05 (-0.28, 0.18)
HD GOLI SC + MTX		1.06 (0.36, 2.71)	1.04 (0.51, 1.73)	0.01 (-0.23, 0.24)
HD INF IV + MTX		1.55 (0.77, 2.74)	1.27 (0.86, 1.70)	0.11 (-0.06, 0.24)
SD ABA IV + MTX	SD ADA SC + MTX	0.92 (0.42, 2.01)	0.95 (0.59, 1.41)	-0.02 (-0.20, 0.17)
SD ADA + MTX		0.89 (0.35, 2.25)	0.94 (0.53, 1.47)	-0.03 (-0.24, 0.20)
SD ETN SC + MTX		0.55 (0.20, 1.54)	0.70 (0.33, 1.25)	-0.14 (-0.34, 0.11)
SD GOLI SC + MTX		1.06 (0.43, 2.63)	1.03 (0.60, 1.56)	0.01 (-0.20, 0.23)
SD RITUX IV + MTX		1.26 (0.56, 2.90)	1.12 (0.72, 1.62)	0.06 (-0.14, 0.25)
LD RITUX IV + MTX		1.39 (0.61, 3.17)	1.17 (0.77, 1.66)	0.08 (-0.12, 0.27)
HD GOLI SC		0.58 (0.23, 1.49)	0.73 (0.37, 1.23)	-0.13 (-0.32, 0.10)
HD GOLI SC + MTX		0.76 (0.30, 1.90)	0.86 (0.47, 1.37)	-0.07 (-0.27, 0.16)
HD INF IV + MTX		1.10 (0.55, 2.48)	1.05 (0.72, 1.54)	0.02 (-0.15, 0.22)
SD ADA + MTX	SD ABA IV + MTX	0.97 (0.33, 2.87)	0.98 (0.53, 1.76)	-0.01 (-0.26, 0.25)
SD ETN SC + MTX		0.60 (0.18, 1.94)	0.73 (0.33, 1.45)	-0.12 (-0.36, 0.16)
SD GOLI SC + MTX		1.15 (0.40, 3.38)	1.08 (0.60, 1.88)	0.03 (-0.22, 0.29)
SD RITUX IV + MTX		1.38 (0.52, 3.75)	1.18 (0.71, 1.97)	0.08 (-0.16, 0.31)
LD RITUX IV + MTX		1.52 (0.56, 4.13)	1.23 (0.75, 2.05)	0.10 (-0.14, 0.33)
HD GOLI SC		0.64 (0.21, 1.90)	0.76 (0.38, 1.44)	-0.11 (-0.34, 0.15)
HD GOLI SC + MTX		0.82 (0.28, 2.43)	0.90 (0.47, 1.63)	-0.05 (-0.29, 0.21)
HD INF IV + MTX		1.20 (0.49, 3.25)	1.10 (0.70, 1.88)	0.05 (-0.17, 0.28)

(Continued)

SD ETN SC + MTX	SD ADA + MTX	0.61 (0.17, 2.22)	0.74 (0.32, 1.61)	-0.11 (-0.38, 0.18)
SD GOLI SC + MTX		1.20 (0.36, 3.86)	1.10 (0.58, 2.09)	0.04 (-0.24, 0.32)
SD RITUX IV + MTX		1.42 (0.47, 4.27)	1.20 (0.69, 2.20)	0.09 (-0.18, 0.34)
LD RITUX IV + MTX		1.57 (0.52, 4.66)	1.25 (0.73, 2.27)	0.11 (-0.16, 0.36)
HD GOLI SC		0.66 (0.19, 2.18)	0.78 (0.37, 1.60)	-0.10 (-0.36, 0.18)
HD GOLI SC + MTX		0.85 (0.26, 2.79)	0.91 (0.46, 1.81)	-0.04 (-0.31, 0.24)
HD INF IV + MTX		1.24 (0.44, 3.72)	1.12 (0.67, 2.09)	0.05 (-0.20, 0.31)
SD GOLI SC + MTX	SD ETN SC + MTX	1.93 (0.54, 6.90)	1.47 (0.71, 3.32)	0.15 (-0.14, 0.42)
SD RITUX IV + MTX		2.31 (0.70, 7.76)	1.61 (0.83, 3.52)	0.20 (-0.09, 0.45)
LD RITUX IV + MTX		2.55 (0.78, 8.44)	1.68 (0.88, 3.66)	0.22 (-0.06, 0.47)
HD GOLI SC		1.06 (0.29, 3.85)	1.04 (0.45, 2.49)	0.01 (-0.27, 0.28)
HD GOLI SC + MTX		1.38 (0.38, 4.96)	1.22 (0.56, 2.84)	0.07 (-0.22, 0.34)
HD INF IV + MTX		2.02 (0.66, 6.69)	1.51 (0.80, 3.37)	0.17 (-0.10, 0.41)
SD RITUX IV + MTX	SD GOLI SC + MTX	1.20 (0.40, 3.59)	1.09 (0.64, 1.93)	0.04 (-0.22, 0.30)
LD RITUX IV + MTX		1.32 (0.44, 3.94)	1.14 (0.68, 2.00)	0.07 (-0.20, 0.32)
HD GOLI SC		0.55 (0.25, 1.20)	0.71 (0.42, 1.11)	-0.14 (-0.31, 0.04)
HD GOLI SC + MTX		0.72 (0.33, 1.55)	0.83 (0.52, 1.28)	-0.08 (-0.26, 0.10)
HD INF IV + MTX		1.04 (0.38, 3.14)	1.02 (0.63, 1.85)	0.01 (-0.23, 0.27)
LD RITUX IV + MTX	SD RITUX IV + MTX	1.10 (0.56, 2.15)	1.05 (0.76, 1.44)	0.02 (-0.14, 0.18)
HD GOLI SC		0.46 (0.15, 1.40)	0.65 (0.32, 1.20)	-0.19 (-0.42, 0.08)
HD GOLI SC + MTX		0.60 (0.20, 1.79)	0.76 (0.40, 1.35)	-0.13 (-0.37, 0.14)
HD INF IV + MTX		0.87 (0.35, 2.43)	0.93 (0.61, 1.56)	-0.04 (-0.25, 0.21)
HD GOLI SC	LD RITUX IV + MTX	0.42 (0.14, 1.28)	0.62 (0.31, 1.14)	-0.21 (-0.44, 0.06)
HD GOLI SC + MTX		0.54 (0.18, 1.64)	0.73 (0.39, 1.28)	-0.15 (-0.39, 0.12)
HD INF IV + MTX		0.79 (0.31, 2.21)	0.90 (0.59, 1.47)	-0.06 (-0.27, 0.19)
HD GOLI SC + MTX	HD GOLI SC	1.30 (0.58, 2.91)	1.18 (0.71, 1.99)	0.06 (-0.12, 0.24)
HD INF IV + MTX		1.89 (0.68, 5.81)	1.44 (0.81, 2.97)	0.15 (-0.09, 0.39)

(Continued)

HD INF IV + MTX	HD GOLI SC + MTX	1.45 (0.53, 4.39)	1.23 (0.72, 2.37)	0.09 (-0.15, 0.34)

Random-effects model	Residual deviance	38.64 vs 35 data-points
	Deviance information criteria	232.262
Fixed-effect model	Residual deviance	40.19 vs 35 data-points
	Deviance information criteria	231.958

ABA: abatacept

ADA: adalimumab

CrI: credible interval

ETN: etanercept

GOLI: golimumab

HD: high dose

INF: infliximab

IV: intravenous

LD: low dose

MP: methylprednisolone

MTX: methotrexate

OR: odds ratio

RD: risk difference

RITUX: rituximab

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 15. Subgroup analysis: Remission, early RA

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
MP + MTX	MTX + PL	1.49 (0.38, 4.45)	1.25 (0.50, 1.95)	0.10 (-0.20, 0.35)
SD INF IV + MTX		1.46 (0.67, 3.13)	1.24 (0.77, 1.75)	0.09 (-0.09, 0.28)

(Continued)

SD ADA + MTX		2.26 (0.79, 6.50)	1.52 (0.86, 2.14)	0.20 (-0.05, 0.42)
SD ETN SC + MTX		1.39 (0.44, 4.40)	1.21 (0.56, 1.94)	0.08 (-0.17, 0.35)
SD RITUX IV + MTX		3.20 (1.24, 8.66)	1.73 (1.13, 2.25)	0.28 (0.05, 0.46)
LD RITUX IV + MTX		3.54 (1.35, 9.45)	1.79 (1.19, 2.29)	0.30 (0.07, 0.47)
HD INF IV + MTX		2.48 (0.99, 6.11)	1.58 (1.00, 2.10)	0.22 (0.00, 0.41)
SD INF IV + MTX	MP + MTX	0.98 (0.42, 2.86)	0.99 (0.69, 1.97)	0.00 (-0.20, 0.22)
SD ADA + MTX		1.52 (0.35, 9.05)	1.21 (0.62, 3.14)	0.10 (-0.24, 0.47)
SD ETN SC + MTX		0.94 (0.20, 5.81)	0.97 (0.42, 2.65)	-0.02 (-0.37, 0.39)
SD RITUX IV + MTX		2.15 (0.54, 12.31)	1.37 (0.79, 3.49)	0.18 (-0.14, 0.53)
LD RITUX IV + MTX		2.38 (0.59, 13.57)	1.42 (0.82, 3.57)	0.20 (-0.12, 0.55)
HD INF IV + MTX		1.66 (0.53, 7.12)	1.25 (0.78, 2.89)	0.12 (-0.14, 0.43)
SD ADA + MTX	SD INF IV + MTX	1.55 (0.42, 5.82)	1.22 (0.64, 2.16)	0.11 (-0.20, 0.39)
SD ETN SC + MTX		0.95 (0.24, 3.89)	0.98 (0.43, 1.88)	-0.01 (-0.32, 0.31)
SD RITUX IV + MTX		2.19 (0.65, 7.86)	1.39 (0.83, 2.34)	0.19 (-0.10, 0.44)
LD RITUX IV + MTX		2.42 (0.71, 8.65)	1.44 (0.86, 2.41)	0.21 (-0.08, 0.46)
HD INF IV + MTX		1.69 (0.71, 4.18)	1.27 (0.85, 1.89)	0.13 (-0.08, 0.32)
SD ETN SC + MTX	SD ADA + MTX	0.62 (0.13, 2.89)	0.80 (0.36, 1.63)	-0.12 (-0.45, 0.24)
SD RITUX IV + MTX		1.41 (0.35, 6.03)	1.14 (0.68, 2.07)	0.08 (-0.23, 0.38)
LD RITUX IV + MTX		1.57 (0.37, 6.56)	1.17 (0.71, 2.12)	0.10 (-0.21, 0.40)
HD INF IV + MTX		1.09 (0.27, 4.34)	1.04 (0.60, 1.91)	0.02 (-0.28, 0.33)
SD RITUX IV + MTX	SD ETN SC + MTX	2.30 (0.53, 10.57)	1.42 (0.78, 3.12)	0.20 (-0.14, 0.51)
LD RITUX IV + MTX		2.55 (0.58, 11.78)	1.47 (0.81, 3.20)	0.22 (-0.12, 0.52)
HD INF IV + MTX		1.77 (0.41, 7.66)	1.30 (0.69, 2.84)	0.14 (-0.20, 0.45)
LD RITUX IV + MTX	SD RITUX IV + MTX	1.10 (0.43, 2.80)	1.03 (0.75, 1.42)	0.02 (-0.17, 0.21)
HD INF IV + MTX		0.77 (0.20, 2.82)	0.91 (0.55, 1.48)	-0.06 (-0.34, 0.23)
HD INF IV + MTX	LD RITUX IV + MTX	0.70 (0.18, 2.60)	0.88 (0.54, 1.41)	-0.08 (-0.35, 0.21)

(Continued)

Random-effects model	Residual deviance	17.42 vs 16 data-points
	Deviance information criteria	107.304
Fixed-effect model	Residual deviance	18.28 vs 16 data-points
	Deviance information criteria	107.435
Note:		

Total participants	2313
Total studies	7
2-arm	5
3-arm	2

ADA: adalimumab

CrI: credible interval

ETN: etanercept

HD: high dose

INF: infliximab

IV: intravenous

LD: low dose

MP: methylprednisolone

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RITUX: rituximab

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 16. Subgroup analysis: Remission, established RA

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC	MTX + PL	0.95 (0.55, 1.64)	0.96 (0.60, 1.48)	-0.01 (-0.07, 0.08)
SD INF IV + MTX		7.01 (1.84, 32.99)	3.46 (1.58, 6.40)	0.42 (0.11, 0.70)
SD ADA SC + MTX		2.55 (1.81, 3.55)	2.02 (1.58, 2.55)	0.17 (0.10, 0.25)
SD ABA IV + MTX		2.32 (1.29, 4.20)	1.90 (1.23, 2.77)	0.15 (0.04, 0.29)
SD GOLI SC + MTX		2.67 (1.25, 5.78)	2.08 (1.20, 3.30)	0.18 (0.03, 0.37)
HD GOLI SC		1.48 (0.67, 3.32)	1.37 (0.71, 2.42)	0.06 (-0.05, 0.23)
HD GOLI SC + MTX		1.91 (0.89, 4.24)	1.65 (0.91, 2.79)	0.11 (-0.02, 0.29)
SD INF IV + MTX	SD ADA SC	7.44 (1.72, 37.88)	3.62 (1.48, 7.89)	0.42 (0.10, 0.71)
SD ADA SC + MTX		2.69 (1.56, 4.57)	2.11 (1.38, 3.32)	0.18 (0.08, 0.26)
SD ABA IV + MTX		2.46 (1.11, 5.46)	1.98 (1.08, 3.62)	0.16 (0.02, 0.31)
SD GOLI SC + MTX		2.82 (1.12, 7.24)	2.17 (1.09, 4.17)	0.19 (0.02, 0.38)
HD GOLI SC		1.56 (0.60, 4.11)	1.43 (0.65, 2.97)	0.07 (-0.07, 0.25)
HD GOLI SC + MTX		2.02 (0.79, 5.25)	1.73 (0.83, 3.48)	0.12 (-0.04, 0.31)
SD ADA SC + MTX	SD INF IV + MTX	0.36 (0.07, 1.45)	0.58 (0.32, 1.27)	-0.25 (-0.56, 0.08)
SD ABA IV + MTX		0.33 (0.06, 1.41)	0.55 (0.27, 1.24)	-0.26 (-0.59, 0.08)
SD GOLI SC + MTX		0.38 (0.07, 1.81)	0.60 (0.27, 1.41)	-0.23 (-0.58, 0.14)
HD GOLI SC		0.21 (0.04, 1.02)	0.40 (0.16, 1.01)	-0.35 (-0.67, 0.01)
HD GOLI SC + MTX		0.27 (0.05, 1.30)	0.48 (0.21, 1.18)	-0.30 (-0.63, 0.06)
SD ABA IV + MTX	SD ADA SC + MTX	0.91 (0.47, 1.80)	0.94 (0.58, 1.45)	-0.02 (-0.16, 0.14)
SD GOLI SC + MTX		1.05 (0.46, 2.43)	1.03 (0.58, 1.70)	0.01 (-0.16, 0.21)
HD GOLI SC		0.58 (0.25, 1.40)	0.68 (0.34, 1.24)	-0.11 (-0.25, 0.07)
HD GOLI SC + MTX		0.75 (0.33, 1.78)	0.82 (0.44, 1.44)	-0.06 (-0.21, 0.13)
SD GOLI SC + MTX	SD ABA IV + MTX	1.15 (0.44, 3.03)	1.10 (0.57, 2.04)	0.03 (-0.17, 0.25)
HD GOLI SC		0.63 (0.24, 1.72)	0.72 (0.34, 1.45)	-0.09 (-0.27, 0.11)
HD GOLI SC + MTX		0.82 (0.31, 2.19)	0.87 (0.43, 1.69)	-0.04 (-0.23, 0.17)
HD GOLI SC	SD GOLI SC + MTX	0.55 (0.27, 1.14)	0.66 (0.38, 1.09)	-0.12 (-0.27, 0.03)
HD GOLI SC + MTX		0.71 (0.36, 1.45)	0.80 (0.49, 1.28)	-0.07 (-0.22, 0.08)

(Continued)

HD GOLI SC + MTX	HD GOLI SC	1.30 (0.62, 2.70)	1.21 (0.70, 2.11)	0.05 (-0.09, 0.19)

Random-effects model	Residual deviance	18.13 vs 19 data-points
	Deviance information criteria	122.691
Fixed-effect model	Residual deviance	18.28 vs 19 data-points
	Deviance information criteria	121.942
Note:		

Total participants	3248
Total studies	8
2-arm	6
3-arm	1
4-arm	1

ABA: abatacept

ADA: adalimumab

CrI: credible interval

GOLI: golimumab

HD: high dose

INF: infliximab

IV: intravenous

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 17. Subgroup analysis 2: Remission, trial duration ≤ 6 months

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
MP + MTX	MTX + PL	8.44 (1.18, 71.50)	3.78 (1.14, 7.10)	0.46 (0.03, 0.78)
SD INF IV + MTX		5.35 (1.00, 34.69)	3.11 (1.00, 6.51)	0.35 (0.00, 0.71)
SD ADA SC + MTX		2.67 (1.47, 5.77)	2.10 (1.36, 3.37)	0.18 (0.06, 0.36)
SD ADA + MTX		2.27 (0.88, 5.98)	1.88 (0.90, 3.40)	0.14 (-0.02, 0.37)
SD GOLI SC + MTX		2.70 (1.07, 6.93)	2.11 (1.06, 3.69)	0.18 (0.01, 0.40)
HD GOLI SC		1.49 (0.56, 3.95)	1.38 (0.61, 2.73)	0.06 (-0.07, 0.26)
HD GOLI SC + MTX		1.93 (0.76, 5.10)	1.68 (0.79, 3.14)	0.11 (-0.04, 0.33)
SD INF IV + MTX	MP + MTX	0.64 (0.22, 1.80)	0.85 (0.51, 1.39)	-0.09 (-0.31, 0.12)
SD ADA SC + MTX		0.32 (0.04, 2.66)	0.56 (0.28, 1.93)	-0.27 (-0.64, 0.20)
SD ADA + MTX		0.27 (0.03, 2.42)	0.50 (0.19, 1.80)	-0.31 (-0.69, 0.18)
SD GOLI SC + MTX		0.32 (0.03, 2.86)	0.56 (0.23, 1.97)	-0.27 (-0.66, 0.22)
HD GOLI SC		0.17 (0.02, 1.60)	0.37 (0.13, 1.39)	-0.39 (-0.75, 0.09)
HD GOLI SC + MTX		0.23 (0.02, 2.06)	0.45 (0.17, 1.63)	-0.34 (-0.71, 0.14)
SD ADA SC + MTX	SD INF IV + MTX	0.51 (0.07, 3.18)	0.68 (0.30, 2.22)	-0.16 (-0.56, 0.24)
SD ADA + MTX		0.42 (0.05, 2.98)	0.61 (0.22, 2.06)	-0.20 (-0.61, 0.22)
SD GOLI SC + MTX		0.50 (0.06, 3.48)	0.68 (0.26, 2.26)	-0.16 (-0.58, 0.26)
HD GOLI SC		0.28 (0.03, 1.95)	0.45 (0.15, 1.60)	-0.28 (-0.67, 0.13)
HD GOLI SC + MTX		0.36 (0.05, 2.49)	0.54 (0.19, 1.87)	-0.23 (-0.63, 0.18)
SD ADA + MTX	SD ADA SC + MTX	0.85 (0.25, 2.55)	0.89 (0.37, 1.78)	-0.04 (-0.28, 0.21)
SD GOLI SC + MTX		1.00 (0.29, 2.97)	1.00 (0.43, 1.93)	0.00 (-0.25, 0.25)
HD GOLI SC		0.55 (0.16, 1.69)	0.65 (0.25, 1.42)	-0.12 (-0.34, 0.11)
HD GOLI SC + MTX		0.72 (0.21, 2.18)	0.80 (0.32, 1.64)	-0.07 (-0.30, 0.17)
SD GOLI SC + MTX	SD ADA + MTX	1.19 (0.31, 4.58)	1.12 (0.46, 2.78)	0.04 (-0.25, 0.31)
HD GOLI SC		0.65 (0.17, 2.57)	0.73 (0.27, 1.99)	-0.08 (-0.34, 0.18)
HD GOLI SC + MTX		0.85 (0.22, 3.31)	0.89 (0.35, 2.32)	-0.03 (-0.30, 0.24)
HD GOLI SC	SD GOLI SC + MTX	0.55 (0.22, 1.36)	0.66 (0.33, 1.24)	-0.11 (-0.29, 0.06)

(Continued)

HD GOLI SC + MTX		0.72 (0.29, 1.77)	0.80 (0.42, 1.47)	-0.07 (-0.25, 0.11)
HD GOLI SC + MTX	HD GOLI SC	1.30 (0.52, 3.29)	1.22 (0.62, 2.43)	0.05 (-0.12, 0.22)

Random-effects model	Residual deviance	13.72 vs 14 data-points
	Deviance information criteria	91.46
Fixed-effect model	Residual deviance	13.64 vs 14 data-points
	Deviance information criteria	91.099
Note:		

Total participants	2058
Total studies	6
2-arm	5
4-arm	1

ADA: adalimumab

CrI: credible interval

GOLI: golimumab

HD: high dose

INF: infliximab

IV: intravenous

MP: methylprednisolone

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 18. Subgroup analysis 2: Remission, trial duration 6-12 months

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
MP + MTX	MTX + PL	0.39 (0.04, 2.98)	0.48 (0.06, 1.86)	-0.16 (-0.30, 0.26)
SD INF IV + MTX		1.52 (0.55, 4.09)	1.31 (0.64, 2.12)	0.09 (-0.11, 0.34)
SD ABA IV + MTX		2.33 (0.84, 6.33)	1.65 (0.88, 2.44)	0.20 (-0.04, 0.43)
SD ETN SC + MTX		1.39 (0.41, 4.64)	1.24 (0.51, 2.26)	0.07 (-0.16, 0.36)
HD INF IV + MTX		2.53 (0.93, 6.85)	1.72 (0.95, 2.50)	0.22 (-0.01, 0.44)
SD INF IV + MTX	MP + MTX	3.89 (0.65, 27.17)	2.69 (0.80, 16.60)	0.24 (-0.10, 0.45)
SD ABA IV + MTX		5.99 (0.63, 63.99)	3.40 (0.80, 26.15)	0.35 (-0.10, 0.61)
SD ETN SC + MTX		3.58 (0.33, 43.76)	2.56 (0.52, 21.27)	0.22 (-0.24, 0.54)
HD INF IV + MTX		6.49 (0.85, 57.16)	3.53 (0.93, 24.88)	0.36 (-0.03, 0.60)
SD ABA IV + MTX	SD INF IV + MTX	1.54 (0.37, 6.33)	1.26 (0.59, 2.74)	0.10 (-0.22, 0.40)
SD ETN SC + MTX		0.91 (0.19, 4.38)	0.95 (0.36, 2.32)	-0.02 (-0.35, 0.33)
HD INF IV + MTX		1.67 (0.62, 4.51)	1.31 (0.79, 2.28)	0.12 (-0.10, 0.33)
SD ETN SC + MTX	SD ABA IV + MTX	0.59 (0.12, 2.83)	0.75 (0.30, 1.72)	-0.13 (-0.44, 0.24)
HD INF IV + MTX		1.09 (0.26, 4.55)	1.04 (0.53, 2.07)	0.02 (-0.30, 0.34)
HD INF IV + MTX	SD ETN SC + MTX	1.83 (0.38, 8.55)	1.38 (0.62, 3.42)	0.15 (-0.22, 0.46)

Random-effects model	Residual deviance	9.119 vs 9 data-points
	Deviance information criteria	62.314
Fixed-effect model	Residual deviance	9.107 vs 9 data-points
	Deviance information criteria	62.28
Note:		

Total participants	1697
Total studies	4

(Continued)

2-arm	3
3-arm	1

ABA: abatacept

CrI: credible interval

ETN: etanercept

HD: high dose

INF: infliximab

IV: intravenous

MP: methylprednisolone

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 19. Subgroup analysis 2: Remission, trial duration > 12 months

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC	MTX + PL	0.92 (0.36, 2.24)	0.95 (0.45, 1.62)	-0.02 (-0.17, 0.19)
SD INF IV + MTX		2.25 (0.68, 9.21)	1.61 (0.77, 2.91)	0.19 (-0.08, 0.50)
SD ADA SC + MTX		2.42 (1.11, 4.66)	1.66 (1.07, 2.25)	0.21 (0.02, 0.36)
SD RITUX IV + MTX		3.21 (1.20, 8.66)	1.87 (1.13, 2.67)	0.28 (0.04, 0.48)
LD RITUX IV + MTX		3.55 (1.32, 9.47)	1.94 (1.20, 2.73)	0.30 (0.06, 0.50)
SD INF IV + MTX	SD ADA SC	2.44 (0.58, 13.68)	1.68 (0.72, 4.48)	0.21 (-0.12, 0.55)
SD ADA SC + MTX		2.63 (1.02, 6.33)	1.75 (1.01, 3.32)	0.23 (0.00, 0.39)
SD RITUX IV + MTX		3.49 (0.93, 14.00)	1.97 (0.96, 4.46)	0.29 (-0.02, 0.55)
LD RITUX IV + MTX		3.85 (1.02, 15.17)	2.05 (1.01, 4.59)	0.32 (0.01, 0.57)
SD ADA SC + MTX	SD INF IV + MTX	1.07 (0.21, 4.09)	1.03 (0.51, 2.14)	0.02 (-0.35, 0.33)
SD RITUX IV + MTX		1.44 (0.25, 6.35)	1.17 (0.55, 2.42)	0.09 (-0.31, 0.42)

(Continued)

LD RITUX IV + MTX		1.59 (0.27, 7.02)	1.21 (0.59, 2.50)	0.11 (-0.29, 0.43)
SD RITUX IV + MTX	SD ADA SC + MTX	1.32 (0.42, 4.83)	1.13 (0.65, 1.94)	0.07 (-0.20, 0.35)
LD RITUX IV + MTX		1.47 (0.46, 5.32)	1.17 (0.69, 1.99)	0.09 (-0.18, 0.36)
LD RITUX IV + MTX	SD RITUX IV + MTX	1.10 (0.42, 2.86)	1.04 (0.71, 1.54)	0.02 (-0.19, 0.23)

Random-effects model	Residual deviance	13.97 vs 12 data-points
	Deviance information criteria	80.022
Fixed-effect model	Residual deviance	15.28 vs 12 data-points
	Deviance information criteria	80.498
Note:		

Total participants	1806
Total studies	5
2-arm	3
3-arm	2

ADA: adalimumab

CrI: credible interval

INF: infliximab

IV: intravenous

LD: low dose

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RITUX: rituximab

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 20. Radiographic progression: main analysis

Treatment	Reference	MD (95% CrI)
MP + MTX	MTX + PL	-2.63 (-14.60, 9.55)
SD ETN SC + MTX		-4.00 (-9.38, 1.64)
SD INF IV + MTX		-3.32 (-10.98, 4.43)
SD ABA IV + MTX		-0.44 (-8.20, 7.31)
HD INF IV + MTX		-3.17 (-10.90, 4.50)
SD ETN SC + MTX	MP + MTX	-1.38 (-14.62, 11.89)
SD INF IV + MTX		-0.71 (-10.12, 8.62)
SD ABA IV + MTX		2.19 (-12.20, 16.56)
HD INF IV + MTX		-0.58 (-12.77, 11.43)
SD INF IV + MTX	SD ETN SC + MTX	0.70 (-8.89, 10.11)
SD ABA IV + MTX		3.54 (-6.06, 13.05)
HD INF IV + MTX		0.84 (-8.77, 10.09)
SD ABA IV + MTX	SD INF IV + MTX	2.85 (-8.09, 13.82)
HD INF IV + MTX		0.10 (-7.58, 7.76)
HD INF IV + MTX	SD ABA IV + MTX	-2.74 (-13.79, 8.14)

Random-effects model	11.23 Residual deviance	vs 11 data-points
	Deviance information criteria	29.311
Fixed-effect model	42.46 Residual deviance	vs 11 data-points
	Deviance information criteria	59.485

ABA: abatacept

CrI: credible interval

ETN: etanercept

HD: high dose

INF: infliximab

IV: intravenous

(Continued)

MD: mean difference

MP: methylprednisolone

MTX: methotrexate

PL: placebo

SC: subcutaneous

SD: standard dose

Appendix 21. Subgroup analysis 2: Radiographic progression, trial duration 6-12 months

Treatment	Reference	MD (95% CrI)
SD ETN SC + MTX	MTX + PL	-5.50 (-7.09, -3.82)
SD INF IV + MTX		-3.30 (-5.46, -1.15)
SD ABA IV + MTX		-0.43 (-2.82, 1.96)
HD INF IV + MTX		-3.20 (-5.35, -1.06)
SD INF IV + MTX	SD ETN SC + MTX	2.21 (-0.58, 4.84)
SD ABA IV + MTX		5.08 (2.14, 7.92)
HD INF IV + MTX		2.30 (-0.46, 4.95)
SD ABA IV + MTX	SD INF IV + MTX	2.88 (-0.36, 6.10)
HD INF IV + MTX		0.10 (-1.84, 2.04)
HD INF IV + MTX	SD ABA IV + MTX	-2.78 (-5.97, 0.46)

Random-effects model	Residual deviance	17.38 vs 9 data-points
	Deviance information criteria	26.794
Fixed-effect model	Residual deviance	40.49 vs 19 data-points
	Deviance information criteria	49.323

Total participants	2144
Total studies	4

(Continued)

2-arm	3
3-arm	1

ABA: abatacept

CrI: credible interval

ETN: etanercept

HD: high dose

INF: infliximab

IV: intravenous

MD: mean difference

MTX: methotrexate

PL: placebo

SC: subcutaneous

SD: standard dose

Appendix 22. Withdrawals due to adverse events: main analysis

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC	MTX	1.32 (0.60, 2.91)	1.31 (0.61, 2.72)	0.01 (-0.01, 0.06)
SD ADA SC + MTX		1.74 (1.00, 3.07)	1.69 (1.00, 2.86)	0.03 (0.00, 0.07)
SD INF IV + MTX		2.10 (1.09, 4.01)	2.02 (1.08, 3.66)	0.04 (0.00, 0.09)
SD ETN SC + MTX		0.89 (0.45, 2.12)	0.89 (0.46, 2.04)	0.00 (-0.02, 0.04)
SD ABA IV + MTX		0.78 (0.26, 2.38)	0.79 (0.26, 2.27)	-0.01 (-0.03, 0.05)
SD GOLI SC + MTX		2.73 (0.73, 12.02)	2.56 (0.73, 8.67)	0.06 (-0.01, 0.27)
SD RITUX IV + MTX		0.38 (0.12, 1.09)	0.39 (0.12, 1.09)	-0.02 (-0.04, 0.00)
LD RITUX IV + MTX		0.44 (0.15, 1.25)	0.45 (0.15, 1.24)	-0.02 (-0.04, 0.01)
HD GOLI SC		0.45 (0.05, 2.80)	0.46 (0.05, 2.63)	-0.02 (-0.04, 0.06)
HD GOLI SC + MTX		3.68 (1.04, 15.81)	3.34 (1.04, 10.44)	0.09 (0.00, 0.33)
HD INF IV + MTX		2.46 (1.10, 5.58)	2.33 (1.09, 4.84)	0.05 (0.00, 0.13)
SD ADA SC + MTX	SD ADA SC	1.31 (0.61, 2.85)	1.29 (0.63, 2.71)	0.01 (-0.03, 0.05)
SD INF IV + MTX		1.60 (0.55, 4.33)	1.56 (0.58, 3.99)	0.03 (-0.04, 0.08)

(Continued)

SD ETN SC + MTX		0.67 (0.24, 2.19)	0.68 (0.26, 2.11)	-0.01 (-0.07, 0.03)
SD ABA IV + MTX		0.59 (0.15, 2.31)	0.60 (0.16, 2.21)	-0.02 (-0.08, 0.04)
SD GOLI SC + MTX		2.07 (0.44, 10.95)	1.96 (0.46, 8.14)	0.05 (-0.04, 0.26)
SD RITUX IV + MTX		0.28 (0.07, 1.06)	0.29 (0.08, 1.06)	-0.03 (-0.09, 0.00)
LD RITUX IV + MTX		0.33 (0.09, 1.24)	0.35 (0.09, 1.23)	-0.03 (-0.09, 0.01)
HD GOLI SC		0.34 (0.03, 2.46)	0.35 (0.04, 2.33)	-0.03 (-0.09, 0.05)
HD GOLI SC + MTX		2.81 (0.62, 14.39)	2.57 (0.64, 9.87)	0.07 (-0.03, 0.32)
HD INF IV + MTX		1.86 (0.61, 5.75)	1.78 (0.63, 5.07)	0.04 (-0.03, 0.13)
SD INF IV + MTX	SD ADA SC + MTX	1.21 (0.50, 2.80)	1.20 (0.52, 2.60)	0.01 (-0.05, 0.07)
SD ETN SC + MTX		0.51 (0.21, 1.44)	0.53 (0.23, 1.41)	-0.03 (-0.07, 0.02)
SD ABA IV + MTX		0.45 (0.13, 1.55)	0.47 (0.14, 1.50)	-0.03 (-0.08, 0.03)
SD GOLI SC + MTX		1.57 (0.37, 7.65)	1.51 (0.39, 5.72)	0.03 (-0.05, 0.25)
SD RITUX IV + MTX		0.22 (0.06, 0.72)	0.23 (0.07, 0.73)	-0.05 (-0.09, -0.01)
LD RITUX IV + MTX		0.25 (0.07, 0.83)	0.27 (0.08, 0.83)	-0.04 (-0.09, -0.01)
HD GOLI SC		0.26 (0.03, 1.74)	0.27 (0.03, 1.68)	-0.04 (-0.09, 0.04)
HD GOLI SC + MTX		2.14 (0.52, 10.03)	2.00 (0.54, 6.90)	0.06 (-0.04, 0.31)
HD INF IV + MTX		1.42 (0.53, 3.80)	1.38 (0.55, 3.36)	0.02 (-0.04, 0.11)
SD ETN SC + MTX	SD INF IV + MTX	0.42 (0.17, 1.31)	0.44 (0.18, 1.29)	-0.04 (-0.09, 0.01)
SD ABA IV + MTX		0.37 (0.10, 1.40)	0.39 (0.11, 1.36)	-0.04 (-0.10, 0.02)
SD GOLI SC + MTX		1.30 (0.30, 6.62)	1.27 (0.32, 4.93)	0.02 (-0.07, 0.24)
SD RITUX IV + MTX		0.18 (0.05, 0.63)	0.19 (0.05, 0.64)	-0.06 (-0.11, -0.02)
LD RITUX IV + MTX		0.21 (0.06, 0.72)	0.22 (0.07, 0.74)	-0.06 (-0.11, -0.01)
HD GOLI SC		0.21 (0.02, 1.53)	0.23 (0.02, 1.48)	-0.06 (-0.11, 0.03)
HD GOLI SC + MTX		1.77 (0.42, 8.77)	1.67 (0.45, 6.00)	0.05 (-0.05, 0.30)
HD INF IV + MTX		1.16 (0.57, 2.58)	1.15 (0.59, 2.34)	0.01 (-0.04, 0.09)
SD ABA IV + MTX	SD ETN SC + MTX	0.88 (0.21, 3.22)	0.88 (0.22, 3.06)	0.00 (-0.05, 0.05)
SD GOLI SC + MTX		3.05 (0.62, 15.53)	2.85 (0.64, 11.38)	0.06 (-0.02, 0.28)
SD RITUX IV + MTX		0.42 (0.10, 1.47)	0.43 (0.11, 1.46)	-0.02 (-0.06, 0.01)

(Continued)

LD RITUX IV + MTX		0.50 (0.12, 1.68)	0.51 (0.13, 1.66)	-0.02 (-0.06, 0.02)
HD GOLI SC		0.50 (0.05, 3.52)	0.50 (0.05, 3.30)	-0.02 (-0.06, 0.06)
HD GOLI SC + MTX		4.15 (0.89, 20.05)	3.74 (0.89, 13.75)	0.09 (-0.01, 0.33)
HD INF IV + MTX		2.76 (0.84, 7.83)	2.60 (0.85, 6.84)	0.05 (-0.01, 0.14)
SD GOLI SC + MTX	SD ABA IV + MTX	3.51 (0.61, 22.37)	3.25 (0.63, 16.78)	0.06 (-0.02, 0.28)
SD RITUX IV + MTX		0.48 (0.10, 2.21)	0.49 (0.10, 2.17)	-0.01 (-0.07, 0.02)
LD RITUX IV + MTX		0.56 (0.12, 2.60)	0.57 (0.13, 2.54)	-0.01 (-0.07, 0.02)
HD GOLI SC		0.56 (0.05, 4.99)	0.57 (0.05, 4.65)	-0.01 (-0.07, 0.07)
HD GOLI SC + MTX		4.75 (0.87, 29.63)	4.25 (0.88, 20.74)	0.09 (-0.01, 0.34)
HD INF IV + MTX		3.14 (0.78, 12.27)	2.95 (0.80, 10.74)	0.06 (-0.01, 0.14)
SD RITUX IV + MTX	SD GOLI SC + MTX	0.14 (0.02, 0.75)	0.15 (0.03, 0.76)	-0.08 (-0.29, -0.01)
LD RITUX IV + MTX		0.16 (0.03, 0.87)	0.18 (0.04, 0.87)	-0.08 (-0.29, 0.00)
HD GOLI SC		0.17 (0.02, 0.77)	0.18 (0.02, 0.79)	-0.07 (-0.25, -0.01)
HD GOLI SC + MTX		1.35 (0.47, 4.03)	1.30 (0.52, 3.44)	0.03 (-0.08, 0.17)
HD INF IV + MTX		0.89 (0.17, 4.27)	0.90 (0.22, 3.85)	-0.01 (-0.23, 0.10)
LD RITUX IV + MTX	SD RITUX IV + MTX	1.17 (0.34, 4.08)	1.17 (0.35, 3.99)	0.00 (-0.02, 0.03)
HD GOLI SC		1.18 (0.11, 10.03)	1.18 (0.11, 9.31)	0.00 (-0.03, 0.08)
HD GOLI SC + MTX		9.97 (1.90, 60.09)	8.74 (1.85, 41.81)	0.11 (0.02, 0.35)
HD INF IV + MTX		6.51 (1.73, 26.09)	6.00 (1.69, 22.81)	0.07 (0.02, 0.16)
HD GOLI SC	LD RITUX IV + MTX	1.01 (0.09, 8.66)	1.01 (0.10, 8.02)	0.00 (-0.03, 0.08)
HD GOLI SC + MTX		8.45 (1.62, 50.37)	7.43 (1.58, 34.71)	0.11 (0.02, 0.35)
HD INF IV + MTX		5.57 (1.53, 22.12)	5.15 (1.49, 19.12)	0.07 (0.02, 0.15)
HD GOLI SC + MTX	HD GOLI SC	8.13 (1.80, 67.37)	7.03 (1.70, 55.97)	0.10 (0.02, 0.31)
HD INF IV + MTX		5.54 (0.73, 58.34)	5.12 (0.75, 51.46)	0.07 (-0.02, 0.15)
HD INF IV + MTX	HD GOLI SC + MTX	0.66 (0.13, 3.06)	0.69 (0.18, 2.78)	-0.04 (-0.29, 0.09)

(Continued)

Random-effects model	Residual deviance	33.71 vs 33 data-points
	Deviance information criteria	179.39
Fixed-effect model	Residual deviance	34.36 vs 33 data-points
	Deviance information criteria	178.816

ABA: abatacept

ADA: adalimumab

CrI: credible interval

ETN: etanercept

GOLI: golimumab

HD: high dose

INF: infliximab

IV: intravenous

LD: low dose

MTX: methotrexate

OR: odds ratio

RD: risk difference

RITUX: rituximab

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 23. Subgroup analysis: Withdrawals due to adverse events, early RA

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA + MTX	MTX + PL	1.08 (0.33, 3.39)	1.08 (0.34, 3.20)	0.00 (-0.02, 0.05)
SD INF IV + MTX		3.34 (1.33, 9.36)	3.12 (1.31, 7.99)	0.06 (0.01, 0.16)
SD RITUX IV + MTX		0.38 (0.11, 1.19)	0.39 (0.12, 1.19)	-0.02 (-0.03, 0.00)
LD RITUX IV + MTX		0.44 (0.13, 1.38)	0.45 (0.13, 1.36)	-0.01 (-0.03, 0.01)
HD INF IV + MTX		3.38 (1.24, 9.99)	3.16 (1.23, 8.32)	0.06 (0.01, 0.18)

(Continued)

SD INF IV + MTX	SD ADA + MTX	3.12 (0.72, 14.66)	2.92 (0.74, 12.66)	0.06 (-0.02, 0.16)
SD RITUX IV + MTX		0.35 (0.07, 1.84)	0.36 (0.07, 1.82)	-0.02 (-0.07, 0.01)
LD RITUX IV + MTX		0.41 (0.08, 2.16)	0.42 (0.08, 2.12)	-0.02 (-0.07, 0.02)
HD INF IV + MTX		3.15 (0.69, 15.71)	2.95 (0.71, 13.18)	0.06 (-0.02, 0.18)
SD RITUX IV + MTX	SD INF IV + MTX	0.11 (0.02, 0.50)	0.12 (0.03, 0.52)	-0.08 (-0.17, -0.02)
LD RITUX IV + MTX		0.13 (0.03, 0.58)	0.14 (0.03, 0.60)	-0.07 (-0.17, -0.02)
HD INF IV + MTX		1.01 (0.42, 2.41)	1.01 (0.45, 2.18)	0.00 (-0.07, 0.09)
LD RITUX IV + MTX	SD RITUX IV + MTX	1.17 (0.32, 4.26)	1.17 (0.32, 4.18)	0.00 (-0.02, 0.02)
HD INF IV + MTX		8.93 (1.93, 45.48)	8.18 (1.88, 38.25)	0.08 (0.02, 0.19)
HD INF IV + MTX	LD RITUX IV + MTX	7.69 (1.65, 38.22)	7.05 (1.61, 32.28)	0.08 (0.02, 0.19)

Random-effects model	Residual deviance	12.76 vs 14 data-points
	Deviance information criteria	71.072
Fixed-effect model	Residual deviance	12.73 vs 14 data-points
	Deviance information criteria	70.632
Note:		

Total participants	2416
Total studies	6
2-arm	4
3-arm	2

ADA: adalimumab

CrI: credible interval

HD: high dose

INF: infliximab

IV: intravenous

LD: low dose

(Continued)

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RITUX: rituximab

RR: risk ratio

SD: standard dose

Appendix 24. Subgroup analysis: Withdrawals due to adverse events, established RA

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC	MTX + PL	1.28 (0.59, 2.71)	1.26 (0.60, 2.51)	0.01 (-0.02, 0.07)
SD ADA SC + MTX		1.62 (0.92, 2.78)	1.57 (0.92, 2.58)	0.03 (0.00, 0.07)
SD ETN SC + MTX		0.78 (0.36, 1.70)	0.79 (0.37, 1.64)	-0.01 (-0.03, 0.03)
SD ABA IV + MTX		0.80 (0.27, 2.31)	0.81 (0.28, 2.18)	-0.01 (-0.04, 0.05)
SD GOLI SC + MTX		2.82 (0.77, 12.17)	2.58 (0.78, 8.25)	0.08 (-0.01, 0.31)
HD GOLI SC		0.46 (0.05, 2.93)	0.47 (0.06, 2.70)	-0.03 (-0.05, 0.07)
HD GOLI SC + MTX		3.78 (1.09, 15.66)	3.32 (1.09, 9.67)	0.11 (0.00, 0.37)
SD ADA SC + MTX	SD ADA SC	1.27 (0.60, 2.65)	1.25 (0.63, 2.50)	0.01 (-0.04, 0.06)
SD ETN SC + MTX		0.61 (0.21, 1.84)	0.63 (0.23, 1.78)	-0.02 (-0.08, 0.03)
SD ABA IV + MTX		0.62 (0.17, 2.36)	0.64 (0.18, 2.23)	-0.02 (-0.09, 0.05)
SD GOLI SC + MTX		2.20 (0.50, 11.82)	2.04 (0.52, 8.26)	0.06 (-0.04, 0.30)
HD GOLI SC		0.36 (0.04, 2.68)	0.37 (0.04, 2.49)	-0.04 (-0.10, 0.06)
HD GOLI SC + MTX		2.96 (0.69, 15.28)	2.63 (0.71, 9.81)	0.10 (-0.03, 0.36)
SD ETN SC + MTX	SD ADA SC + MTX	0.48 (0.19, 1.26)	0.50 (0.21, 1.24)	-0.04 (-0.09, 0.01)
SD ABA IV + MTX		0.49 (0.15, 1.66)	0.51 (0.16, 1.60)	-0.04 (-0.09, 0.04)
SD GOLI SC + MTX		1.74 (0.43, 8.42)	1.64 (0.45, 5.88)	0.05 (-0.06, 0.29)
HD GOLI SC		0.28 (0.03, 1.99)	0.30 (0.03, 1.88)	-0.05 (-0.11, 0.05)
HD GOLI SC + MTX		2.33 (0.60, 10.88)	2.11 (0.62, 6.93)	0.09 (-0.04, 0.35)
SD ABA IV + MTX	SD ETN SC + MTX	1.02 (0.27, 3.82)	1.02 (0.28, 3.57)	0.00 (-0.05, 0.07)

(Continued)

SD GOLI SC + MTX		3.59 (0.79, 18.91)	3.25 (0.80, 13.13)	0.09 (-0.01, 0.32)
HD GOLI SC		0.59 (0.06, 4.38)	0.60 (0.06, 4.01)	-0.01 (-0.06, 0.08)
HD GOLI SC + MTX		4.84 (1.10, 25.03)	4.19 (1.10, 15.89)	0.12 (0.01, 0.38)
SD GOLI SC + MTX	SD ABA IV + MTX	3.55 (0.65, 21.41)	3.20 (0.68, 15.21)	0.09 (-0.03, 0.32)
HD GOLI SC		0.58 (0.05, 4.83)	0.59 (0.06, 4.45)	-0.01 (-0.08, 0.08)
HD GOLI SC + MTX		4.81 (0.91, 28.67)	4.15 (0.92, 18.54)	0.12 (-0.01, 0.38)
HD GOLI SC	SD GOLI SC + MTX	0.16 (0.02, 0.76)	0.19 (0.02, 0.78)	-0.10 (-0.30, -0.01)
HD GOLI SC + MTX		1.34 (0.48, 3.87)	1.28 (0.54, 3.16)	0.03 (-0.10, 0.19)
HD GOLI SC + MTX	HD GOLI SC	8.17 (1.85, 64.91)	6.82 (1.72, 51.09)	0.13 (0.03, 0.35)

Random-effects model	Residual deviance	14.15 vs 15 data-points
	Deviance information criteria	91.568
Fixed-effect model	Residual deviance	13.9 vs 15 data-points
	Deviance information criteria	90.89
Note:		

Total participants	3667
Total studies	6
2-arm	4
3-arm	1
4-arm	1

ABA: abatacept

ADA: adalimumab

CrI: credible interval

ETN: etanercept

GOLI: golimumab

HD: high dose

(Continued)

IV: intravenous

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 25. Subgroup analysis 2: Withdrawals due to adverse events, trial duration ≤ 6 months

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA + MTX	MTX + PL	1.49 (0.70, 2.95)	1.47 (0.70, 2.83)	0.01 (-0.01, 0.04)
SD GOLI SC + MTX		2.78 (0.71, 13.07)	2.66 (0.72, 10.41)	0.04 (-0.01, 0.21)
HD GOLI SC		0.46 (0.05, 2.90)	0.47 (0.05, 2.78)	-0.01 (-0.03, 0.04)
HD GOLI SC + MTX		3.71 (1.03, 16.68)	3.46 (1.03, 12.51)	0.06 (0.00, 0.25)
SD GOLI SC + MTX	SD ADA + MTX	1.88 (0.41, 10.56)	1.82 (0.43, 8.46)	0.03 (-0.03, 0.20)
HD GOLI SC		0.31 (0.03, 2.33)	0.32 (0.03, 2.25)	-0.02 (-0.06, 0.03)
HD GOLI SC + MTX		2.52 (0.59, 13.57)	2.38 (0.61, 10.29)	0.05 (-0.02, 0.24)
HD GOLI SC	SD GOLI SC + MTX	0.16 (0.02, 0.83)	0.18 (0.02, 0.84)	-0.05 (-0.20, -0.01)
HD GOLI SC + MTX		1.33 (0.44, 4.18)	1.30 (0.47, 3.68)	0.02 (-0.07, 0.14)
HD GOLI SC + MTX	HD GOLI SC	8.06 (1.73, 65.65)	7.30 (1.66, 57.20)	0.08 (0.02, 0.24)
Random-effects model	Residual deviance	10.15 vs 10 data-points		
	Deviance information criteria	55.097		
Fixed-effect model	Residual deviance	10.3 vs 10 data-points		
	Deviance information criteria	54.868		

(Continued)

Note:

Total participants	2175
Total studies	4
2-arm	3
4-arm	1

ADA: adalimumab

CrI: credible interval

GOLI: golimumab

HD: high dose

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 26. Subgroup analysis 2: Withdrawals due to adverse events, trial duration 6-12 months

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC	MTX + PL	1.32 (0.47, 3.73)	1.30 (0.48, 3.34)	0.01 (-0.02, 0.10)
SD ADA SC + MTX		1.71 (0.62, 4.77)	1.66 (0.63, 4.10)	0.03 (-0.02, 0.14)
SD INF IV + MTX		3.32 (1.21, 10.13)	2.99 (1.20, 7.59)	0.09 (0.01, 0.25)
SD ETN SC + MTX		0.90 (0.42, 2.84)	0.91 (0.43, 2.64)	0.00 (-0.03, 0.07)
SD ABA IV + MTX		0.80 (0.23, 2.74)	0.81 (0.24, 2.55)	-0.01 (-0.04, 0.07)
HD INF IV + MTX		3.36 (1.18, 10.50)	3.02 (1.16, 7.70)	0.09 (0.01, 0.27)
SD ADA SC + MTX	SD ADA SC	1.30 (0.48, 3.57)	1.27 (0.51, 3.22)	0.02 (-0.05, 0.10)
SD INF IV + MTX		2.52 (0.60, 11.66)	2.30 (0.63, 9.08)	0.08 (-0.04, 0.24)
SD ETN SC + MTX		0.68 (0.20, 3.39)	0.70 (0.23, 3.16)	-0.02 (-0.10, 0.06)

(Continued)

SD ABA IV + MTX		0.60 (0.12, 2.97)	0.62 (0.14, 2.78)	-0.02 (-0.11, 0.06)
HD INF IV + MTX		2.55 (0.58, 12.10)	2.32 (0.62, 9.14)	0.08 (-0.04, 0.25)
SD INF IV + MTX	SD ADA SC + MTX	1.94 (0.46, 8.92)	1.81 (0.51, 6.93)	0.06 (-0.07, 0.23)
SD ETN SC + MTX		0.53 (0.16, 2.63)	0.55 (0.18, 2.48)	-0.03 (-0.14, 0.05)
SD ABA IV + MTX		0.47 (0.09, 2.27)	0.49 (0.11, 2.15)	-0.04 (-0.15, 0.05)
HD INF IV + MTX		1.97 (0.45, 9.14)	1.83 (0.50, 6.99)	0.06 (-0.07, 0.24)
SD ETN SC + MTX	SD INF IV + MTX	0.27 (0.07, 1.26)	0.30 (0.10, 1.24)	-0.09 (-0.25, 0.02)
SD ABA IV + MTX		0.24 (0.05, 1.16)	0.27 (0.06, 1.14)	-0.10 (-0.26, 0.01)
HD INF IV + MTX		1.02 (0.38, 2.60)	1.02 (0.44, 2.22)	0.00 (-0.11, 0.13)
SD ABA IV + MTX	SD ETN SC + MTX	0.88 (0.16, 3.53)	0.89 (0.17, 3.28)	0.00 (-0.08, 0.07)
HD INF IV + MTX		3.72 (0.75, 13.88)	3.33 (0.77, 10.45)	0.10 (-0.02, 0.27)
HD INF IV + MTX	SD ABA IV + MTX	4.24 (0.83, 22.80)	3.76 (0.84, 17.35)	0.10 (-0.01, 0.27)

Random-effects model	Residual deviance	13.88 vs 14 data-points
	Deviance information criteria	81.811
Fixed-effect model	Residual deviance	14.15 vs 14 data-points
	Deviance information criteria	81.916
Note:		

Total participants	3029
Total studies	6
2-arm	4
3-arm	2

ABA: abatacept

ADA: adalimumab

CrI: credible interval

ETN: etanercept

(Continued)

HD: high dose

INF: infliximab

IV: intravenous

MTX: methotrexate

OR: odds ratio

PL: placebo

RD: risk difference

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 27. Serious adverse events: main analysis

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
MP + MTX	MTX	0.79 (0.21, 2.95)	0.81 (0.23, 2.53)	-0.02 (-0.07, 0.13)
SD ADA SC + MTX		0.99 (0.63, 1.58)	0.99 (0.65, 1.50)	0.00 (-0.03, 0.04)
SD INF IV + MTX		1.33 (0.70, 2.59)	1.29 (0.72, 2.28)	0.03 (-0.03, 0.11)
SD ABA IV + MTX		0.99 (0.41, 2.35)	0.99 (0.44, 2.10)	0.00 (-0.05, 0.10)
SD ETN SC + MTX		3.68 (0.86, 20.72)	2.97 (0.87, 8.05)	0.18 (-0.01, 0.56)
SD GOLI SC + MTX		0.91 (0.31, 2.61)	0.92 (0.33, 2.30)	-0.01 (-0.06, 0.11)
SD RITUX IV + MTX		0.75 (0.35, 1.60)	0.76 (0.37, 1.52)	-0.02 (-0.06, 0.05)
LD RITUX IV + MTX		0.86 (0.41, 1.83)	0.87 (0.43, 1.70)	-0.01 (-0.05, 0.06)
HD GOLI SC		0.42 (0.11, 1.44)	0.44 (0.12, 1.39)	-0.05 (-0.08, 0.03)
HD GOLI SC + MTX		0.91 (0.31, 2.64)	0.92 (0.33, 2.32)	-0.01 (-0.06, 0.11)
HD INF IV + MTX		1.29 (0.63, 2.65)	1.25 (0.65, 2.32)	0.02 (-0.03, 0.11)
SD ADA SC + MTX	MP + MTX	1.25 (0.31, 5.05)	1.23 (0.37, 4.63)	0.02 (-0.14, 0.08)
SD INF IV + MTX		1.67 (0.54, 5.29)	1.59 (0.59, 4.78)	0.04 (-0.08, 0.11)
SD ABA IV + MTX		1.24 (0.26, 5.96)	1.22 (0.30, 5.27)	0.01 (-0.14, 0.13)
SD ETN SC + MTX		4.68 (0.64, 39.87)	3.64 (0.69, 18.15)	0.19 (-0.05, 0.58)
SD GOLI SC + MTX		1.14 (0.21, 6.28)	1.12 (0.25, 5.47)	0.01 (-0.15, 0.14)

(Continued)

SD RITUX IV + MTX		0.94 (0.21, 4.24)	0.94 (0.25, 3.91)	0.00 (-0.15, 0.08)
LD RITUX IV + MTX		1.08 (0.24, 4.86)	1.07 (0.28, 4.42)	0.00 (-0.15, 0.10)
HD GOLI SC		0.52 (0.08, 3.18)	0.54 (0.10, 2.98)	-0.03 (-0.18, 0.06)
HD GOLI SC + MTX		1.14 (0.20, 6.21)	1.13 (0.24, 5.39)	0.01 (-0.15, 0.14)
HD INF IV + MTX		1.62 (0.43, 6.25)	1.55 (0.48, 5.50)	0.04 (-0.10, 0.13)
SD INF IV + MTX	SD ADA SC + MTX	1.34 (0.60, 2.98)	1.30 (0.63, 2.61)	0.03 (-0.04, 0.12)
SD ABA IV + MTX		1.00 (0.37, 2.65)	1.00 (0.40, 2.36)	0.00 (-0.07, 0.10)
SD ETN SC + MTX		3.72 (0.80, 21.85)	2.99 (0.82, 8.75)	0.18 (-0.02, 0.56)
SD GOLI SC + MTX		0.91 (0.28, 2.89)	0.92 (0.31, 2.53)	-0.01 (-0.08, 0.12)
SD RITUX IV + MTX		0.75 (0.31, 1.81)	0.77 (0.33, 1.70)	-0.02 (-0.08, 0.05)
LD RITUX IV + MTX		0.86 (0.36, 2.06)	0.87 (0.39, 1.91)	-0.01 (-0.07, 0.07)
HD GOLI SC		0.42 (0.10, 1.55)	0.45 (0.11, 1.49)	-0.05 (-0.10, 0.04)
HD GOLI SC + MTX		0.91 (0.28, 2.91)	0.92 (0.31, 2.55)	-0.01 (-0.08, 0.12)
HD INF IV + MTX		1.30 (0.55, 3.03)	1.26 (0.58, 2.64)	0.02 (-0.05, 0.12)
SD ABA IV + MTX	SD INF IV + MTX	0.74 (0.25, 2.19)	0.77 (0.28, 1.99)	-0.03 (-0.12, 0.08)
SD ETN SC + MTX		2.78 (0.57, 17.16)	2.29 (0.61, 7.21)	0.15 (-0.06, 0.54)
SD GOLI SC + MTX		0.68 (0.19, 2.37)	0.71 (0.22, 2.12)	-0.03 (-0.13, 0.09)
SD RITUX IV + MTX		0.56 (0.20, 1.51)	0.59 (0.24, 1.45)	-0.05 (-0.14, 0.04)
LD RITUX IV + MTX		0.65 (0.24, 1.73)	0.67 (0.27, 1.63)	-0.04 (-0.13, 0.05)
HD GOLI SC		0.32 (0.07, 1.27)	0.34 (0.08, 1.24)	-0.07 (-0.16, 0.02)
HD GOLI SC + MTX		0.68 (0.20, 2.35)	0.71 (0.22, 2.11)	-0.03 (-0.13, 0.10)
HD INF IV + MTX		0.97 (0.48, 1.95)	0.97 (0.52, 1.79)	0.00 (-0.07, 0.07)
SD ETN SC + MTX	SD ABA IV + MTX	3.75 (0.68, 25.21)	2.99 (0.72, 10.77)	0.17 (-0.04, 0.56)
SD GOLI SC + MTX		0.92 (0.23, 3.65)	0.92 (0.26, 3.19)	-0.01 (-0.12, 0.12)
SD RITUX IV + MTX		0.75 (0.24, 2.41)	0.77 (0.27, 2.25)	-0.02 (-0.12, 0.06)
LD RITUX IV + MTX		0.86 (0.28, 2.75)	0.87 (0.31, 2.53)	-0.01 (-0.11, 0.08)
HD GOLI SC		0.42 (0.09, 1.94)	0.45 (0.10, 1.84)	-0.05 (-0.15, 0.05)
HD GOLI SC + MTX		0.92 (0.23, 3.62)	0.93 (0.26, 3.18)	-0.01 (-0.12, 0.12)

(Continued)

HD INF IV + MTX		1.31 (0.43, 4.03)	1.27 (0.47, 3.51)	0.02 (-0.09, 0.13)
SD GOLI SC + MTX	SD ETN SC + MTX	0.24 (0.03, 1.47)	0.31 (0.07, 1.40)	-0.18 (-0.57, 0.04)
SD RITUX IV + MTX		0.20 (0.03, 1.04)	0.26 (0.07, 1.04)	-0.19 (-0.58, 0.00)
LD RITUX IV + MTX		0.23 (0.04, 1.19)	0.29 (0.09, 1.17)	-0.18 (-0.57, 0.02)
HD GOLI SC		0.11 (0.01, 0.76)	0.15 (0.03, 0.79)	-0.22 (-0.60, -0.02)
HD GOLI SC + MTX		0.24 (0.03, 1.49)	0.31 (0.08, 1.41)	-0.18 (-0.57, 0.04)
HD INF IV + MTX		0.35 (0.05, 1.78)	0.42 (0.13, 1.66)	-0.15 (-0.54, 0.06)
SD RITUX IV + MTX	SD GOLI SC + MTX	0.82 (0.22, 3.05)	0.84 (0.26, 2.83)	-0.01 (-0.13, 0.07)
LD RITUX IV + MTX		0.95 (0.26, 3.48)	0.95 (0.30, 3.19)	0.00 (-0.13, 0.09)
HD GOLI SC		0.47 (0.12, 1.59)	0.49 (0.13, 1.54)	-0.04 (-0.14, 0.03)
HD GOLI SC + MTX		1.00 (0.34, 2.95)	1.00 (0.37, 2.69)	0.00 (-0.09, 0.09)
HD INF IV + MTX		1.42 (0.40, 5.16)	1.37 (0.44, 4.48)	0.03 (-0.10, 0.13)
LD RITUX IV + MTX	SD RITUX IV + MTX	1.15 (0.53, 2.50)	1.14 (0.56, 2.33)	0.01 (-0.05, 0.07)
HD GOLI SC		0.56 (0.12, 2.41)	0.58 (0.13, 2.27)	-0.03 (-0.10, 0.06)
HD GOLI SC + MTX		1.22 (0.33, 4.49)	1.20 (0.35, 3.88)	0.01 (-0.07, 0.14)
HD INF IV + MTX		1.73 (0.61, 4.97)	1.65 (0.64, 4.29)	0.04 (-0.04, 0.14)
HD GOLI SC	LD RITUX IV + MTX	0.49 (0.11, 2.09)	0.51 (0.12, 1.97)	-0.04 (-0.12, 0.05)
HD GOLI SC + MTX		1.06 (0.29, 3.90)	1.06 (0.31, 3.39)	0.00 (-0.09, 0.13)
HD INF IV + MTX		1.50 (0.53, 4.30)	1.45 (0.57, 3.71)	0.03 (-0.06, 0.13)
HD GOLI SC + MTX	HD GOLI SC	2.14 (0.62, 8.36)	2.03 (0.64, 7.41)	0.04 (-0.03, 0.14)
HD INF IV + MTX		3.08 (0.73, 13.81)	2.84 (0.76, 11.82)	0.07 (-0.02, 0.17)
HD INF IV + MTX	HD GOLI SC + MTX	1.42 (0.40, 5.13)	1.37 (0.44, 4.47)	0.03 (-0.10, 0.13)

Random-effects model	Residual deviance	27.66 vs 28 data-points
	Deviance information criteria	171.724

(Continued)

Fixed-effect model	Residual deviance	28.69 vs 28 data-points
	Deviance information criteria	171.488

ABA: abatacept

ADA: adalimumab

CrI: credible interval

ETN: etanercept

GOLI: golimumab

HD: high dose

INF: infliximab

IV: intravenous

LD: low dose

MP: methylprednisolone

MTX: methotrexate

OR: odds ratio

RD: risk difference

RITUX: rituximab

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 28. Subgroup analysis: Serious adverse events, early RA

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
MP + MTX	MTX	0.79 (0.18, 3.37)	0.80 (0.20, 2.78)	-0.02 (-0.08, 0.16)
SD INF IV + MTX		1.34 (0.60, 2.92)	1.30 (0.63, 2.51)	0.03 (-0.04, 0.13)
SD ADA SC + MTX		0.70 (0.30, 1.79)	0.72 (0.33, 1.67)	-0.03 (-0.07, 0.06)
SD ETN SC + MTX		3.69 (0.77, 23.15)	2.95 (0.79, 8.62)	0.18 (-0.02, 0.58)
SD RITUX IV + MTX		0.75 (0.29, 1.91)	0.77 (0.31, 1.76)	-0.02 (-0.07, 0.07)
LD RITUX IV + MTX		0.86 (0.34, 2.19)	0.87 (0.36, 1.98)	-0.01 (-0.06, 0.09)
HD INF IV + MTX		1.29 (0.53, 3.17)	1.26 (0.55, 2.66)	0.02 (-0.04, 0.15)

(Continued)

SD INF IV + MTX	MP + MTX	1.69 (0.50, 5.93)	1.60 (0.56, 5.30)	0.04 (-0.09, 0.13)
SD ADA SC + MTX		0.89 (0.17, 5.18)	0.89 (0.21, 4.72)	-0.01 (-0.18, 0.09)
SD ETN SC + MTX		4.79 (0.56, 48.00)	3.66 (0.61, 21.26)	0.19 (-0.07, 0.59)
SD RITUX IV + MTX		0.95 (0.17, 5.42)	0.95 (0.21, 4.84)	0.00 (-0.18, 0.10)
LD RITUX IV + MTX		1.09 (0.19, 6.12)	1.08 (0.24, 5.41)	0.01 (-0.17, 0.12)
HD INF IV + MTX		1.64 (0.37, 7.44)	1.56 (0.43, 6.37)	0.04 (-0.12, 0.16)
SD ADA SC + MTX	SD INF IV + MTX	0.52 (0.17, 1.84)	0.55 (0.20, 1.73)	-0.05 (-0.16, 0.05)
SD ETN SC + MTX		2.79 (0.48, 20.47)	2.28 (0.53, 8.16)	0.15 (-0.08, 0.56)
SD RITUX IV + MTX		0.56 (0.17, 1.89)	0.59 (0.20, 1.76)	-0.05 (-0.16, 0.06)
LD RITUX IV + MTX		0.64 (0.19, 2.18)	0.67 (0.23, 1.98)	-0.04 (-0.15, 0.08)
HD INF IV + MTX		0.97 (0.41, 2.34)	0.97 (0.45, 2.07)	0.00 (-0.09, 0.10)
SD ETN SC + MTX	SD ADA SC + MTX	5.31 (0.84, 39.41)	4.08 (0.86, 15.36)	0.21 (-0.01, 0.60)
SD RITUX IV + MTX		1.08 (0.27, 3.60)	1.08 (0.30, 3.24)	0.00 (-0.09, 0.10)
LD RITUX IV + MTX		1.24 (0.32, 4.15)	1.22 (0.35, 3.65)	0.01 (-0.08, 0.12)
HD INF IV + MTX		1.87 (0.49, 6.11)	1.76 (0.53, 5.05)	0.05 (-0.06, 0.17)
SD RITUX IV + MTX	SD ETN SC + MTX	0.20 (0.03, 1.25)	0.26 (0.06, 1.22)	-0.20 (-0.60, 0.02)
LD RITUX IV + MTX		0.23 (0.03, 1.43)	0.30 (0.07, 1.37)	-0.19 (-0.59, 0.03)
HD INF IV + MTX		0.35 (0.05, 2.14)	0.43 (0.11, 1.90)	-0.16 (-0.56, 0.09)
LD RITUX IV + MTX		1.15 (0.45, 2.95)	1.14 (0.48, 2.69)	0.01 (-0.06, 0.09)
HD INF IV + MTX	SD RITUX IV + MTX	1.72 (0.48, 6.34)	1.64 (0.52, 5.28)	0.04 (-0.06, 0.17)
HD INF IV + MTX	LD RITUX IV + MTX	1.50 (0.42, 5.43)	1.44 (0.46, 4.52)	0.03 (-0.08, 0.16)

Random-effects model	Residual deviance	16.68 vs 16 data-points
	Deviance information criteria	100.878
Fixed-effect model	Residual deviance	17.38 vs 16 data-points

(Continued)

	Deviance information criteria	100.951

ADA: adalimumab

CrI: credible interval

ETN: etanercept

HD: high dose

INF: infliximab

IV: intravenous

LD: low dose

MP: methylprednisolone

MTX: methotrexate

OR: odds ratio

RD: risk difference

RITUX: rituximab

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 29. Subgroup analysis: Serious adverse events, established RA

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC + MTX	MTX	1.19 (0.68, 2.12)	1.17 (0.70, 1.96)	0.01 (-0.03, 0.07)
SD ABA IV + MTX		0.99 (0.42, 2.34)	0.99 (0.44, 2.12)	0.00 (-0.05, 0.09)
SD GOLI SC + MTX		0.91 (0.31, 2.59)	0.91 (0.34, 2.30)	-0.01 (-0.06, 0.10)
HD GOLI SC		0.42 (0.11, 1.42)	0.44 (0.12, 1.37)	-0.05 (-0.08, 0.03)
HD GOLI SC + MTX		0.90 (0.30, 2.58)	0.91 (0.32, 2.29)	-0.01 (-0.06, 0.10)
SD ABA IV + MTX	SD ADA SC + MTX	0.83 (0.29, 2.30)	0.85 (0.32, 2.09)	-0.01 (-0.09, 0.09)
SD GOLI SC + MTX		0.76 (0.23, 2.49)	0.78 (0.25, 2.23)	-0.02 (-0.10, 0.10)
HD GOLI SC		0.35 (0.09, 1.32)	0.38 (0.10, 1.29)	-0.06 (-0.13, 0.02)
HD GOLI SC + MTX		0.76 (0.22, 2.50)	0.78 (0.25, 2.23)	-0.02 (-0.10, 0.10)
SD GOLI SC + MTX	SD ABA IV + MTX	0.92 (0.24, 3.52)	0.92 (0.27, 3.11)	-0.01 (-0.11, 0.11)

(Continued)

HD GOLI SC		0.42 (0.09, 1.85)	0.45 (0.10, 1.77)	-0.04 (-0.14, 0.04)
HD GOLI SC + MTX		0.91 (0.23, 3.52)	0.92 (0.26, 3.10)	-0.01 (-0.11, 0.11)
HD GOLI SC	SD GOLI SC + MTX	0.46 (0.12, 1.59)	0.49 (0.13, 1.54)	-0.04 (-0.13, 0.03)
HD GOLI SC + MTX		0.99 (0.34, 2.96)	0.99 (0.37, 2.71)	0.00 (-0.09, 0.09)
HD GOLI SC + MTX	HD GOLI SC	2.14 (0.62, 8.28)	2.04 (0.64, 7.42)	0.04 (-0.03, 0.13)

Random-effects model	Residual deviance	10.55 vs 12 data-points
	Deviance information criteria	71.193
Fixed-effect model	Residual deviance	10.13 vs 12 data-points
	Deviance information criteria	70.371

ABA: abatacept

ADA: adalimumab

CrI: credible interval

GOLI: golimumab

HD: high dose

IV: intravenous

MTX: methotrexate

OR: odds ratio

RD: risk difference

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 30. Subgroup analysis: Serious adverse events, trial duration ≤ 6 months

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC + MTX	MTX	0.96 (0.54, 1.75)	0.96 (0.56, 1.66)	0.00 (-0.04, 0.05)
SD GOLI SC + MTX		0.90 (0.27, 2.95)	0.91 (0.29, 2.57)	-0.01 (-0.06, 0.12)

(Continued)

HD GOLI SC		0.42 (0.10, 1.55)	0.44 (0.11, 1.49)	-0.04 (-0.08, 0.04)
HD GOLI SC + MTX		0.90 (0.27, 2.96)	0.91 (0.29, 2.59)	-0.01 (-0.06, 0.12)
SD GOLI SC + MTX	SD ADA SC + MTX	0.94 (0.24, 3.50)	0.95 (0.26, 3.04)	0.00 (-0.07, 0.12)
HD GOLI SC		0.43 (0.09, 1.81)	0.45 (0.10, 1.72)	-0.04 (-0.10, 0.04)
HD GOLI SC + MTX		0.93 (0.25, 3.48)	0.94 (0.27, 3.02)	0.00 (-0.07, 0.12)
HD GOLI SC	SD GOLI SC + MTX	0.46 (0.11, 1.76)	0.48 (0.12, 1.70)	-0.03 (-0.14, 0.03)
HD GOLI SC + MTX		1.00 (0.30, 3.32)	1.00 (0.33, 3.02)	0.00 (-0.10, 0.09)
HD GOLI SC + MTX	HD GOLI SC	2.14 (0.57, 9.09)	2.05 (0.60, 8.11)	0.03 (-0.03, 0.14)

Random-effects model	Residual deviance	12.67 vs 12 data-points
	Deviance information criteria	71.031
Fixed-effect model	Residual deviance	14.37 vs 12 data-points
	Deviance information criteria	71.625

ADA: adalimumab

CrI: credible interval

GOLI: golimumab

HD: high dose

MTX: methotrexate

OR: odds ratio

RD: risk difference

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 31. Subgroup analysis 2: Serious adverse events, trial duration 6-12 months

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD INF IV + MTX	MTX	1.36 (0.48, 3.85)	1.33 (0.50, 3.19)	0.02 (-0.04, 0.16)

(Continued)

SD ABA IV + MTX		0.99 (0.32, 3.00)	1.00 (0.34, 2.63)	0.00 (-0.05, 0.12)
SD ETN SC + MTX		3.75 (0.76, 24.29)	3.11 (0.78, 11.06)	0.16 (-0.02, 0.52)
HD INF IV + MTX		1.31 (0.47, 3.68)	1.28 (0.49, 3.09)	0.02 (-0.04, 0.15)
SD ABA IV + MTX	SD INF IV + MTX	0.73 (0.16, 3.33)	0.75 (0.19, 2.91)	-0.02 (-0.16, 0.10)
SD ETN SC + MTX		2.77 (0.42, 23.12)	2.34 (0.48, 11.31)	0.13 (-0.09, 0.50)
HD INF IV + MTX		0.97 (0.35, 2.64)	0.97 (0.40, 2.34)	0.00 (-0.10, 0.09)
SD ETN SC + MTX	SD ABA IV + MTX	3.80 (0.54, 32.89)	3.13 (0.59, 16.13)	0.15 (-0.06, 0.51)
HD INF IV + MTX		1.32 (0.29, 6.02)	1.29 (0.33, 5.00)	0.02 (-0.10, 0.15)
HD INF IV + MTX	SD ETN SC + MTX	0.35 (0.04, 2.30)	0.41 (0.08, 2.04)	-0.13 (-0.50, 0.09)

Random-effects model	Residual deviance	7.06 vs 7 data-points
	Deviance information criteria	46.793
Fixed-effect model	Residual deviance	7.085 vs 7 data-points
	Deviance information criteria	46.847

ABA: abatacept

CrI: credible interval

ETN: etanercept

HD: high dose

INF: infliximab

IV: intravenous

MTX: methotrexate

OR: odds ratio

RD: risk difference

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 32. Subgroup analysis 2: Serious adverse events, trial duration > 12 months

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC + MTX	MTX	1.17 (0.33, 4.27)	1.15 (0.37, 3.11)	0.02 (-0.09, 0.24)
SD INF IV + MTX		1.28 (0.23, 7.23)	1.23 (0.26, 4.46)	0.03 (-0.11, 0.35)
SD RITUX IV + MTX		0.75 (0.27, 2.14)	0.77 (0.29, 1.88)	-0.03 (-0.10, 0.11)
LD RITUX IV + MTX		0.86 (0.30, 2.45)	0.88 (0.33, 2.08)	-0.02 (-0.09, 0.13)
SD INF IV + MTX	SD ADA SC + MTX	1.09 (0.13, 9.33)	1.07 (0.18, 5.96)	0.01 (-0.25, 0.34)
SD RITUX IV + MTX		0.64 (0.12, 3.28)	0.68 (0.17, 2.79)	-0.05 (-0.27, 0.12)
LD RITUX IV + MTX		0.73 (0.14, 3.75)	0.76 (0.19, 3.12)	-0.03 (-0.26, 0.14)
SD RITUX IV + MTX	SD INF IV + MTX	0.58 (0.08, 4.29)	0.63 (0.13, 3.64)	-0.06 (-0.37, 0.13)
LD RITUX IV + MTX		0.67 (0.09, 4.90)	0.71 (0.14, 4.05)	-0.04 (-0.36, 0.16)
LD RITUX IV + MTX	SD RITUX IV + MTX	1.15 (0.40, 3.25)	1.13 (0.45, 2.80)	0.01 (-0.09, 0.12)

Random-effects model	Residual deviance	7.115 vs 7 data-points
	Deviance information criteria	44.854
Fixed-effect model	Residual deviance	7.118 vs 7 data-points
	Deviance information criteria	44.858

ADA: adalimumab

CrI: credible interval

INF: infliximab

IV: intravenous

LD: low dose

MTX: methotrexate

OR: odds ratio

RD: risk difference

RITUX: rituximab

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 33. Cancer: main analysis

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC	MTX	1.13 (0.22, 5.31)	1.13 (0.22, 5.17)	0.00 (-0.01, 0.03)
SD ADA SC + MTX		0.76 (0.23, 2.33)	0.76 (0.23, 2.32)	0.00 (-0.01, 0.01)
SD INF IV + MTX		1.02 (0.02, 65.27)	1.02 (0.02, 51.84)	0.00 (-0.01, 0.20)
SD ETN SC + MTX		0.97 (0.23, 4.29)	0.97 (0.23, 4.21)	0.00 (-0.01, 0.02)
SD GOLI SC + MTX		0.48 (0.02, 6.01)	0.48 (0.02, 5.82)	0.00 (-0.01, 0.03)
SD RITUX IV + MTX		0.40 (0.07, 1.80)	0.40 (0.07, 1.79)	0.00 (-0.01, 0.01)
LD RITUX IV + MTX		0.85 (0.21, 3.23)	0.85 (0.22, 3.18)	0.00 (-0.01, 0.02)
HD GOLI SC + MTX		0.48 (0.03, 5.68)	0.48 (0.03, 5.52)	0.00 (-0.01, 0.03)
SD ADA SC + MTX	SD ADA SC	0.67 (0.13, 3.49)	0.67 (0.14, 3.47)	0.00 (-0.03, 0.01)
SD INF IV + MTX		0.94 (0.01, 80.23)	0.94 (0.01, 63.96)	0.00 (-0.03, 0.20)
SD ETN SC + MTX		0.87 (0.10, 7.28)	0.87 (0.11, 7.17)	0.00 (-0.03, 0.02)
SD GOLI SC + MTX		0.43 (0.01, 8.57)	0.43 (0.02, 8.32)	0.00 (-0.03, 0.03)
SD RITUX IV + MTX		0.34 (0.04, 3.27)	0.34 (0.04, 3.25)	0.00 (-0.03, 0.01)
LD RITUX IV + MTX		0.75 (0.10, 6.36)	0.76 (0.10, 6.27)	0.00 (-0.03, 0.02)
HD GOLI SC + MTX		0.43 (0.02, 8.44)	0.43 (0.02, 8.20)	0.00 (-0.03, 0.03)
SD INF IV + MTX	SD ADA SC + MTX	1.39 (0.02, 103.70)	1.39 (0.02, 81.40)	0.00 (-0.01, 0.20)
SD ETN SC + MTX		1.27 (0.21, 8.58)	1.27 (0.21, 8.42)	0.00 (-0.01, 0.02)
SD GOLI SC + MTX		0.64 (0.02, 9.91)	0.64 (0.02, 9.64)	0.00 (-0.01, 0.03)
SD RITUX IV + MTX		0.52 (0.07, 3.52)	0.52 (0.07, 3.48)	0.00 (-0.01, 0.01)
LD RITUX IV + MTX		1.12 (0.18, 6.58)	1.12 (0.18, 6.48)	0.00 (-0.01, 0.02)
HD GOLI SC + MTX		0.64 (0.03, 9.27)	0.64 (0.03, 9.04)	0.00 (-0.01, 0.03)
SD ETN SC + MTX	SD INF IV + MTX	0.93 (0.01, 67.47)	0.93 (0.02, 66.48)	0.00 (-0.20, 0.02)
SD GOLI SC + MTX		0.44 (0.00, 55.00)	0.44 (0.00, 52.63)	0.00 (-0.20, 0.03)
SD RITUX IV + MTX		0.37 (0.00, 27.52)	0.37 (0.01, 27.33)	0.00 (-0.20, 0.01)
LD RITUX IV + MTX		0.81 (0.01, 61.16)	0.81 (0.01, 60.36)	0.00 (-0.20, 0.02)
HD GOLI SC + MTX		0.43 (0.00, 47.80)	0.43 (0.00, 46.89)	0.00 (-0.20, 0.03)

(Continued)

SD GOLI SC + MTX	SD ETN SC + MTX	0.49 (0.02, 9.58)	0.49 (0.02, 9.30)	0.00 (-0.02, 0.03)
SD RITUX IV + MTX		0.41 (0.04, 3.33)	0.41 (0.04, 3.30)	0.00 (-0.02, 0.01)
LD RITUX IV + MTX		0.88 (0.12, 6.43)	0.88 (0.12, 6.34)	0.00 (-0.02, 0.02)
HD GOLI SC + MTX		0.50 (0.02, 8.15)	0.50 (0.02, 7.94)	0.00 (-0.02, 0.03)
SD RITUX IV + MTX	SD GOLI SC + MTX	0.80 (0.04, 23.51)	0.81 (0.04, 23.36)	0.00 (-0.03, 0.01)
LD RITUX IV + MTX		1.79 (0.10, 51.11)	1.79 (0.10, 50.34)	0.00 (-0.03, 0.02)
HD GOLI SC + MTX		0.99 (0.05, 27.09)	0.99 (0.05, 26.72)	0.00 (-0.02, 0.02)
LD RITUX IV + MTX	SD RITUX IV + MTX	2.16 (0.45, 12.82)	2.15 (0.45, 12.69)	0.00 (0.00, 0.02)
HD GOLI SC + MTX		1.24 (0.05, 24.10)	1.24 (0.05, 23.38)	0.00 (-0.01, 0.03)
HD GOLI SC + MTX	LD RITUX IV + MTX	0.56 (0.03, 9.61)	0.56 (0.03, 9.33)	0.00 (-0.02, 0.03)

Random-effects model	Residual deviance	19.83 vs 25 data-points
	Deviance information criteria	98.38
Fixed-effect model	Residual deviance	19.89 vs 25 data-points
	Deviance information criteria	98.272

ADA: adalimumab

CrI: credible interval

ETN: etanercept

GOLI: golimumab

HD: high dose

INF: infliximab

IV: intravenous

LD: low dose

MTX: methotrexate

OR: odds ratio

RD: risk difference

RITUX: rituximab

(Continued)

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 34. Subgroup analysis: Cancer, established RA

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC	MTX	1.28 (0.24, 7.33)	1.27 (0.24, 7.04)	0.00 (-0.01, 0.04)
SD ADA SC + MTX		1.01 (0.24, 4.38)	1.01 (0.24, 4.29)	0.00 (-0.01, 0.02)
SD ETN SC + MTX		1.00 (0.17, 5.44)	1.00 (0.18, 5.25)	0.00 (-0.01, 0.03)
SD GOLI SC + MTX		0.50 (0.03, 6.25)	0.50 (0.03, 6.04)	0.00 (-0.01, 0.04)
HD GOLI SC		0.50 (0.03, 5.68)	0.50 (0.03, 5.49)	0.00 (-0.01, 0.03)
SD ADA SC + MTX	SD ADA SC	0.79 (0.13, 4.65)	0.79 (0.14, 4.59)	0.00 (-0.04, 0.01)
SD ETN SC + MTX		0.78 (0.07, 8.78)	0.78 (0.07, 8.51)	0.00 (-0.04, 0.03)
SD GOLI SC + MTX		0.38 (0.01, 8.84)	0.38 (0.01, 8.49)	-0.01 (-0.05, 0.03)
HD GOLI SC		0.39 (0.01, 7.71)	0.39 (0.01, 7.49)	-0.01 (-0.05, 0.03)
SD ETN SC + MTX	SD ADA SC + MTX	0.99 (0.10, 8.92)	0.99 (0.10, 8.64)	0.00 (-0.02, 0.04)
SD GOLI SC + MTX		0.49 (0.02, 8.80)	0.49 (0.02, 8.48)	0.00 (-0.02, 0.04)
HD GOLI SC		0.50 (0.02, 7.99)	0.50 (0.02, 7.72)	0.00 (-0.02, 0.03)
SD GOLI SC + MTX	SD ETN SC + MTX	0.50 (0.02, 10.88)	0.50 (0.02, 10.47)	0.00 (-0.04, 0.04)
HD GOLI SC		0.50 (0.02, 9.65)	0.50 (0.02, 9.37)	0.00 (-0.04, 0.03)
HD GOLI SC	SD GOLI SC + MTX	1.00 (0.05, 20.51)	1.00 (0.05, 20.18)	0.00 (-0.03, 0.03)

Random-effects model	Residual deviance	11.45 vs 12 data-points
	Deviance information criteria	52.311
Fixed-effect model	Residual deviance	11.63 vs 12 data-points
	Deviance information criteria	52.347

(Continued)

ADA: adalimumab

CrI: credible interval

ETN: etanercept

GOLI: golimumab

HD: high dose

MTX: methotrexate

OR: odds ratio

RD: risk difference

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 35. Subgroup analysis 2: Cancer, trial duration < 6 months

Treatment	Reference	OR (95% CrI)	RR (95% CrI)	RD % (95% CrI)
SD ADA SC + MTX	MTX	1.04 (0.24, 4.62)	1.04 (0.24, 4.57)	0.00 (-0.01, 0.01)
SD GOLI SC + MTX		0.41 (0.01, 5.97)	0.42 (0.01, 5.83)	0.00 (-0.01, 0.02)
HD GOLI SC		0.40 (0.01, 6.24)	0.40 (0.01, 6.08)	0.00 (-0.01, 0.03)
SD GOLI SC + MTX	SD ADA SC + MTX	0.39 (0.01, 8.06)	0.39 (0.01, 7.84)	0.00 (-0.02, 0.03)
HD GOLI SC		0.37 (0.01, 8.57)	0.37 (0.01, 8.32)	0.00 (-0.02, 0.03)
HD GOLI SC	SD GOLI SC + MTX	0.99 (0.02, 42.56)	0.99 (0.02, 41.79)	0.00 (-0.02, 0.02)

Random-effects model	Residual deviance	9.036 vs 11 data-points
	Deviance information criteria	40.215
Fixed-effect model	Residual deviance	9.2 vs 11 data-points
	Deviance information criteria	40.214

ADA: adalimumab

CrI: credible interval

GOLI: golimumab

(Continued)

HD: high dose

MTX: methotrexate

OR: odds ratio

RD: risk difference

RR: risk ratio

SC: subcutaneous

SD: standard dose

Appendix 36. Summary of safety warnings from regulatory agencies

Abatacept

No recent warnings have been issued with regard to abatacept. On the product label of abatacept, the FDA warns against known safety implications reporting, "In controlled clinical trials, patients receiving concomitant abatacept and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively). Concurrent administration of a TNF antagonist with abatacept has been associated with an increased risk of serious infections and no statistically significant additional benefit over use of the TNF antagonists alone" (FDA 2007). Furthermore, the FDA reports that, "rare occurrences of anaphylaxis or anaphylactoid reactions have been observed in two of 2,688 patients treated with abatacept in clinical trials" (FDA 2017). Trials have also shown that, "COPD patients treated with abatacept developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea" (FDA 2017).

The effects of abatacept on pregnant women, pediatric patients, and the development of malignancies is "not yet fully understood" (FDA 2017). The European Medicines Agency (EMA) reports the adverse reactions in patients treated with abatacept, ranking the occurrences of such reactions as very common (≤ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and very rare (< 1/10,000). EMA 2009a reports increase in blood pressure, abnormal liver function test (transaminases increased) and headaches are very common adverse reactions. Dizziness, cough, rash including dermatitis, diarrhea, nausea, dyspepsia, abdominal pain, lower respiratory tract infection (including bronchitis), urinary tract infection, herpes simplex, upper respiratory tract infection, hypertension, flushing, fatigue and asthenia are common (EMA 2009a). Overall, "the most commonly reported adverse events (occurring in 10% or more of patients) were headaches, upper respiratory tract infection, nasopharyngitis, and nausea. The adverse events most commonly resulting in clinical intervention were due to infection" (FDA 2017).

Adalimumab

The updated FDA label for adalimumab reports "Serious infections, sepsis, tuberculosis and cases of opportunistic infections, including fatalities, have been reported with the use of TNF blocking agents including Humira® (adalimumab)" (FDA 2017a). "Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Hospitalization or fatal outcomes associated with infections have been reported" (EMA 2009b). Furthermore, hepatitis B reactivation has been shown to be associated with adalimumab treatment (Health Canada 2006a). The FDA reports, "As observed with other TNF blocking agents, tuberculosis associated with the administration of Humira® in clinical trials has been reported" (FDA 2017a).

In rare instances, adalimumab has been associated with, "new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease including multiple sclerosis" (EMA 2009b). Furthermore, "In the controlled portions of clinical trials of some TNF-blocking agents, including Humira, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients" (FDA 2017a).

"Some of these hepatosplenic T-cell lymphomas have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine used for Crohn's disease". Thus, the risk of the development of hepatosplenic T-cell lymphoma cannot be excluded for patients treated with adalimumab (EMA 2009b). Though the causal relationship of hematological reactions and the use of adalimumab remain unclear as of 2008, the FDA label states, "Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents". Furthermore, the FDA reports "Treatment with Humira® (adalimumab) may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome" (FDA 2017a).

Anakinra

Anakinra leads to an increased rate of infections (2%) versus placebo (less than 1%). Following the EMA standard of classification of frequency of the occurrence of "undesirable effects" mentioned above, neutropenia and serious infection requiring hospitalization were common (between 1/10 and 1/100) and headaches and injection site reactions were very common occurring in 1/10 or more

patients treated with anakinra (EMA 2004). "A… clinical trial sponsored by Amgen Inc. showed a higher incidence of serious infection and of neutropenia in anakinra and etanercept combination group than patients receiving Enbrel (etanercept) alone and higher than observed in previous trials where Kineret (anakinra) was used alone (EMA 2003), therefore, the use of etanercept and anakinra is not recommended as it leads to safety complications)". Furthermore, the FDA reports that "Hypersensitivity reactions associated with Kineret (anakinra) administration are rare" (FDA 2016). Moreover, the FDA reports the effects of anakinra on the hematologic conditions of patients stating that, "In placebo-controlled studies with Kineret® (anakinra), treatment was associated with small reductions in the mean values for total white blood count, platelets, and absolute neutrophil count (ANC), and a small increase in the mean eosinophil differential percentage" (FDA 2016). With regard to the development of malignancies for patients treated with anakinra, trials show that, "twenty-one malignancies of various types were observe in 2531 RA patients treated in clnical trials with Kineret® for up to 50 months. The observed rates and incidences were similar to those expected for the population studied." (FDA 2016).

Etanercept

In the post-marketing reports of etanercept, "Infections, including serious infections leading to hospitalization or death, have been observed in patients treated with Enbrel® (etanercept)" (FDA 2016a). Furthermore, "Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with Enbrel® than with TNF-blocking monoclonal antibodies. Nonetheless, post-marketing cases of tuberculosis reactivation have been reported for TNF blockers, including Enbrel® (etanercept). Patients receiving Enbrel® should be monitored closely for signs and symptoms of active tuberculosis. The possibility of tuberculosis should be considered, especially in patients who have travelled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. All patients treated with Enbrel® should have a thorough history taken prior to initiating therapy" (FDA 2016a). This finding is also stated in an important health warning issued by Health Canada in 2006 (Health Canada 2006a).

Furthemore, etanercept has been associated with the risk of histoplasmosis and other invasive fungal infections. Health Canada 2009 states, "...although no histoplasmosis infections were reported among 17,696 patients from the United States and Canada who were treated with Enbrel®, in 38 clinical trials and four cohort studies involving all authorized indications, post marketing cases of serious and sometimes fatal fungal infections, including histoplasmosis, have been reported with TNF blockers, including Enbrel®." The FDA also outlines the risk of nervous system complications stating, "nervous system complications such as multiple sclerosis, seizures, or inflammation of the nerves of the eyes have occurred in rare cases" (FDA 2016a).

Infections, including serious infections leading to hospitalization or death, have been observed in patients treated with Enbrel® (etanercept) (FDA 2016a). The FDA reports on the risk of malignancies for patients on etanercept treatment, stating "Patients have been observed in clinical trials with Enbrel® for over five years. Among 4462 rheumatoid arthritis patients treated with Enbrel® in clinical trials for a mean of 27 months (approximately 10,000 patient-years of therapy), lymphomas were observed for a rate of 0.09 cases per 100 patient-years. This is 3-fold higher than the rate of lymphomas expected in the general population based on the Surveillance, Epidemiology, and End Results Database. Rare reports of pancytopenia including aplastic anemia, some with a fatal outcome, have been reported in patients treated with Enbrel®" (FDA 2016a). The FDA also reports, "Treatment with Enbrel® may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome or autoimmune hepatitis which may resolve following withdrawal of Enbrel®" (FDA 2016a).

The use of etanercept has also been associated with the relapse of hepatitis B (Health Canada 2006a).

Infliximab

In its recent revised report on infliximab, the EMA reports on the risk of infusion reactions and hypersensitivity, stating, "An infusion-related reaction was defined in clinical studies as any adverse event occurring during an infusion or within 1 to 2 hours after an infusion. In clinical studies, approximately 20% of infliximab-treated patients compared with approximately 10% of placebo-treated patients experienced an infusion-related effect. Approximately 3% of patients discontinued treatment due to infusions reactions" (EMA 2009a). Infliximab is also associated with the relapse of hepatitis B as reported by Health Canada in 2006 (Health Canada 2006a). "Opportunistic infections have been reported in patients treated with infliximab, suggesting that host defence against infection is compromised. It should be noted that suppression of TNF-alpha may also mask symptoms of infection such as fever." There is also a possible association between infliximab and heptosplenix T-Cell lymphoma in pediatric and young adult patients with Crohn's disease (Health Canada 2006b).

"In a study designed to evaluate Remicade® (infliximab) in congestive heart failure (CHF), 150 patients with moderate to severe (NYHA class II-IV) CHF were treated with three infusions of Remicade 5mg/ kg, or placebo over six weeks. Higher incidences of mortality and hospitalization for worsening heart failure were seen in those patients treated with Remicade®, especially those treated with the higher dose of 10mg/kg. At present 7 out of 101 patients treated with Remicade® have died compared to no deaths among 49 patients on placebo" (EMA 2001). In a May 2009 revision of the Remicade label, the FDA warns, "Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving TNF-blocking agents. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported. Patients have frequently presented with disseminated rather than localized disease, and are often taking concomitant immunosuppressants such as methotrexate or corticosteroids with Remicade®" (FDA 2015a). In an investigation of neurological events, EMA reports "Infliximab and other agents that inhibit TNF-alpha have been associated in rare cases with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and peripheral demyelinating disorders, including Guillain-Barré syndrome" (EMA 2009a).

Evidence of infliximab associated with lymphoma states that "In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients… In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately 4-fold higher than expected in the general population. Patients with Crohn's disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy" (FDA 2015a).

TNF-blockers as a group

In 2008, the FDA issued a safety alert regarding anti-TNF biologics, which stated that the risk of pulmonary and disseminated histoplasmosis, coccidioidomycosis, blastomycosis and other opportunistic infections were not consistently recognized in patients taking tumor necrosis factor-alpha blockers (TNF blockers including etanercept, adalimumab, infliximab or certolizumab), which resulted in the delay of proper antifungal treatment and at times led to death (FDA 2008a). The FDA reviewed 240 reports of histoplasmosis, an infection caused by the fungus Histoplasma capsulatum, in patients being treated with Enbrel, Humira, or Remicade. The majority of the reports involved people in the Ohio River and Mississippi River valleys (the fungus is commonly found in those areas). In at least 21 of the reports, histoplasmosis was initially not recognized by healthcare professionals, and antifungal treatment was delayed. Twelve of those patients died. The FDA recommended that for patients at risk of histoplasmosis and other invasive fungal infections, clinicians should consider empiric antifungal treatment until the pathogen(s) are identified.

Rituximab

The FDA provides its most recent safety information for Rituxan® (rituximab) from 2014. Rituxan was found to be associated with progressive multifocal leukoencephalopathy. FDA and Genentech notified: "A third case of progressive multifocal leukoencephalopathy (PML) has been reported in a patient with rheumatoid arthritis treated with Rituxan." In view of this event, Genentech has advised physicians to have high index of suspicion for PML stated as "Physicians should consider PML in any patient being treated with Rituxan who presents with new onset neurologic manifestations. Consultation with a neurologist, brain MRI, and lumbar puncture should be considered as clinically indicated. In patients who develop PML, Rituxan should be discontinued." (FDA 2014). Another event associated with Rituxan was notified in a FDA label from 2008. In this label, the possible safety complications of Rituxan® use included "tumor lysis syndrome which necessitates clinicians to administer prophylaxis and monitor patients renal function, hepatitis B reactivation with fulminant hepatitis, which can sometimes (be) fatal and the risk of progressive multifocal leukoencephalopathy" (Drugs 2006).

FDA and Genentech informed healthcare professionals of important emerging safety information about Rituxan®. "Two patients died after being treated with Rituxan® for systemic lupus erythematosus (SLE). Rituxan® is approved for the above indication and is prescribed off-label for other serious diseases and conditions such as SLE. The cause of death was progressive multifocal leukoencephalopathy, a viral infection of the brain (that is caused by reactivated JC virus which is present in about 80% of adults" (FDA 2006). Further risks include "cardiac arrhythmias and angina" which can be life threatening, and "bowel obstruction and perforation" (FDA 2016a). Health Canada 2006a also provided warnings of bowel obstruction and perforation, "Reports of abdominal pain, bowel obstruction, and perforation, in some cases leading to death, have been observed in patients receiving Rituxan®. The majority of reports, including all deaths, have occurred in patients receiving Rituxan in combination with chemotherapy for NHL ((non-Hodgkin's Lymphoma)) indication. A causal relationship has not been established".

Tofacitinib

In 2015, the FDA issued a Risk Evaluation and Mitigation Strategy (REMS) warning related to tofacitinib highlighting the "Risk of serious infections, malignancies, decreases in peripheral lymphocyte counts, neutrophil counts, hemoglobin, and increases in lipid parameters in peripheral blood with XELJANZ (tofacitinib)" (FDA 2015).

WHAT'S NEW

Date	Event	Description
15 September 2015	New search has been performed	Updated, description: new search with 14 new studies
15 September 2015	New citation required and conclusions have changed	New citation: conclusions changed. Description: original review of biologics in RA split into four by patient population: 1. MTX-naive; 2. biologic + MTX/other DMARDs in MTX/other DMARD failure; 3. biologic monotherapy in MTX/other DMARD failure; and

Date	Event	Description
		4. biologic-experienced. This review will focus on people with RA who are MTX-naive.

HISTORY

Review first published: Issue 5, 2017

Date	Event	Description
1 March 2010	Amended	Odds ratios have been used in the network meta-analyses. See 'Published notes' for details.
25 February 2010	Amended	CMSG ID: C187-R

CONTRIBUTIONS OF AUTHORS

JS - study concept
JS, GW - protocol development
JS, PT, GW, ETG - protocol editing
JS, GW, ETG - data extraction
JS, AM - study quality rating
AH, GW, JS, AM- data analysis
JS - first draft of the review and NMA
All authors - revision of the manuscript, and approval of the final version

DECLARATIONS OF INTEREST

JS - JS has received research grants from Takeda and Savient and consultant fees from Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta and Allergan pharmaceuticals, WebMD, UBM LLC and the American College of Rheumatology. JS serves as the principal investigator for an investigator-initiated study funded by Horizon pharmaceuticals through a grant to DINORA, Inc., a 501 (c)(3) entity. JS is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 36 companies; a member of the American College of Rheumatology's (ACR) Annual Meeting Planning Committee (AMPC); Chair of the ACR Meet-the-Professor, Workshop and Study Group Subcommittee; and a member of the Veterans Affairs Rheumatology Field Advisory Committee.
AH - none
AM - none
EG - none
RB - RB is a Principal Investigator and Chair of the Management Committee of the Australian Rheumatology Association Database (ARAD). The Australian Rheumatology Association receives ongoing unrestricted educational grants from Abbvie, AstraZeneca, Bristol-Myers Squibb, Celgene, Pfizer and Sanofi to support ARAD
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NOTES

We used risk ratios in the Abstract, 'Summary of findings' table and Plain language summary for ease of interpretation. Throughout the rest of the review and NMA, we used odds ratios derived from the NMA.

INDEX TERMS

Medical Subject Headings (MeSH)

Abatacept [therapeutic use]; Adalimumab [therapeutic use]; Antibodies, Monoclonal [therapeutic use]; Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Bayes Theorem; Biological Products [*therapeutic use]; Etanercept [therapeutic use]; Infliximab [therapeutic use]; Methotrexate [*therapeutic use]; Methylprednisolone [therapeutic use]; Network Meta-Analysis; Piperidines [*therapeutic use]; Pyrimidines [*therapeutic use]; Pyrroles [*therapeutic use]; Randomized Controlled Trials as Topic; Rituximab [therapeutic use]

MeSH check words

Adult; Humans