Adalimumab for treating rheumatoid arthritis (Review)

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[Intervention Review]

Adalimumab for treating rheumatoid arthritis

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ABSTRACT

Background

Adalimumab is a fully human anti-TNFalpha monoclonal antibody. Published studies indicate that its use in patients with RA can be effective and safe.

Objectives

The aim of this review was to assess the efficacy and safety of adalimumab in the treatment of RA.

Search methods

Electronic databases were searched up to August, 2004: MEDLINE, CINAHL, EBM Reviews (CDSR, ACP Journal Club, DARE and CENTRAL) and Health STAR. Conference proceedings were hand searched and pharmaceutical companies were contacted to obtain additional unpublished data from published trials. Adalimumab was searched as a text word as it is not currently indexed. The search was not limited by language, year of publication or type of publication.

Selection criteria

All randomised controlled trials (RCTs) or controlled clinical trials (CCTs) comparing adalimumab alone or in combination with DMARDs to placebo or other DMARDs.

Data collection and analysis

Two reviewers independently collected the data in a standardized form and assessed the methodological quality of the trial using validated criteria. Outcome measures included ACR and EULAR responses, DAS 28 and components of ACR response and radiographic data. Safety data were also included. Continuous data were reported as weighted mean difference (WMD) with 95% confidence interval (95%CI), absolute benefit (AB) and relative difference (RD). Dichotomous outcomes were reported as relative risk (RR) with 95% CI, absolute risk difference (ARD) or risk difference (RDiff) with 95%CI and number needed to treat (NNT) or to harm (NNH). When significant heterogeneity was not found, data were pooled.

Main results

Six studies with 2381 patients were included in this review. Two comparisons were done: A. adalimumab subcutaneously (sc) + methotrexate (or DMARDs) versus placebo sc + methotrexate (or DMARDs). B. adalimumab sc in monotherapy versus placebo sc. In the comparison A, with adalimumab 40 mg every other week (e.o.w.), the RR to achieve an ACR 20 response at 24 weeks ranged in the included studies from 1.52 to 4.63, and the NNT ranged from 1.9 to 5.4. The RR (95%CI) to achieve an ACR 50 response was 4.63 (3.04-7.05), and the NNT was 3.0 (95%CI 2.0-6.0). The RR (95%CI) to achieve an ACR 70 response was 5.14 (3.14-8.41) and the number needed to treat was 7.0 (95%CI 5.0-13.0). At 52 weeks, the RRs (95%CI) to achieve an ACR 20, 50, and 70 response were 2.46 (1.87-3.22), 4.37 (2.77-6.91), and 5.15 (2.60-10.22), with NNTs of 2.9, 3.1, and 5.3, respectively. At 52 weeks, adalimumab 40 mg e.o.w. and 20 mg every week (e.w.) significantly slowed the radiological progression including Sharp modified index, erosion score, and joint space score (only with 40 mg e.o.w.). In the comparison B, with adalimumab 40 mg e.o w., the RRs to achieve an ACR 20, 50, and 70 response at 24/26 weeks were 1.91 (1.17-3.10), 2.84 (1.58-5.12), and 7.33 (2.25-33.90) with NNTs of 5.0 (95%CI 3.0-9.0), 7.0 (4.0-20.0), and 9.0 (3.0-38.0), respectively. In most of the analysed studies and comparisons, there were not significant differences in safety outcomes between adalimumab and control groups. The development of positive antinuclear antibodies was significantly more frequent in adalimumab patients than in placebo patients. Serious infections were significantly more frequent in adalimumab patients in only one study (Keystone 2004) with a RR (95%CI) of 7.64(1.02-57.18) and a NNH of 30.2.

Authors' conclusions

On the basis of the studies reviewed here, adalimumab in combination with methotrexate is efficacious and safe in the treatment of the rheumatoid arthritis. Adalimumab 40 mg sc e.o.w. and 20 mg e.w. slows the radiographic progression at 52 weeks. Adalimumab in combination with DMARDs other than methotrexate is also efficacious and safe, even though data from one only study are available and the number of patients in each group is low. Adalimumab in monotherapy is efficacious and safe in the treatment of the rheumatoid arthritis but the effect size is lower than with combined therapy.

PLAIN LANGUAGE SUMMARY

Adalimumab for rheumatoid arthritis

How well does adalimumab work to treat rheumatoid arthritis and how safe is it?

To answer this question, scientists analyzed six high quality studies. The studies tested over 2300 people who had rheumatoid arthritis for more than 10 years. People had either injections of adalimumab or fake injections. Some studies also tested people taking methotrexate in combination with adalimumab or the fake injections. This Cochrane Review provides the best evidence we have today.

What is rheumatoid arthritis and how can adalimumab help?

Rheumatoid arthritis is a disease in which the body's immune system attacks its own healthy tissues. The attack happens mostly in the joints of the feet and hands and causes redness, pain, swelling, and heat around the affected joints. Adalimumab is a "biologic" that is injected into the body to decrease pain and swelling and slow the progress of rheumatoid arthritis. Adalimumab is a new drug that was approved for injection at a dose of 40 mg every other week. It is usually prescribed when other disease modifying anti-rheumatic drugs (DMARDs) do not work well.

How well did adalimumab work?

More people improved with all doses of adalimumab plus methotrexate than with fake injections plus methotrexate. After 24 weeks:

- 43 out of 100 people showed a 50% improvement with 40 mg of adalimumab every other week plus methotrexate
- 9 out of 100 people showed a 50% improvement with fake injections plus methotrexate

This means that 34 more people out of 100 benefited from receiving adalimumab plus methotrexate than fake injections plus methotrexate.

More people had improved symptoms with adalimumab alone than with fake injections, but the improvement was not at much as when adalimumab was taken in combination with methotrexate.

After 52 weeks, x-rays showed that 20 mg of adalimumab every week or 40 mg every other week slowed joint damage more than fake injections.

Were there any side effects?

Minor side effects included reactions where the needle was injected, headaches, allergy-like symptoms, and colds. Some people went to hospital because of serious side effects. Most side effects occurred about the same amount for people taking adalimumab and people taking fake injections.

- 5 out of 100 people had serious side effects with 40 mg of adalimumab every other week plus methotrexate
- 7 out of 100 people had serious side effects with fake injections plus methotrexate

This means that 2 more people out of 100 had a serious side effect from receiving fake injections plus methotrexate than adalimumab plus methotrexate.

One study showed that people who received adalimumab had more serious infections such as tuberculosis and cancer than people who took fake injections. Long-term side effects still need to be studied.

What is the bottom line?

There is "Gold" level evidence (www.cochranemsk.org) that in people with long-standing rheumatoid arthritis who do not respond to DMARDs, adalimumab at 40 mg every other week plus methotrexate decreases pain and swelling.

BACKGROUND

Rheumatoid arthritis (RA) is a systemic inflammatory disease associated with significant morbidity, disability and impaired quality of life. Disease-modifying anti-rheumatic drugs (DMARDs) have been shown to reduce disease activity, to slow disease progression (i.e. reduce the rate of new joint erosions) and to improve patients' quality of life as measured by standard instruments. However, most patients do only experience a partial benefit on traditional DMARDs and many are unable to tolerate these agents for long periods of time. It has been found that Tumour necrosis factor (TNF) alpha has a critical role in the pathogenesis of RA and its blockade has proven to be effective in the treatment of the disease.

However, the use of anti-TNFalpha agents is limited by their high costs and the uncertainty about the long-time adverse events. There are three approved anti-TNF agents, Infliximab - a human murine chimeric anti-TNFalpha monoclonal antibody-, Etanercept - a soluble TNFalpha-receptor-, and Adalimumab-a fully human anti-TNFalpha monoclonal antibody. Infliximab and etanercept have been shown to substantially and rapidly improve RA symptoms and to slow radiographic progression (Blumenauer 2003a, Blumenauer 2003b).

Adalimumab (Humira) is a biological agent that has recently been introduced and approved for the treatment of refractory RA in a dose of 40 mg administered as subcutaneous injection every other week. Adalimumab should be used in combination with methotrexate but it can be used alone when the treatment with

methotrexate is not appropriate. There are studies that provide information about the combination of adalimumab with DMARDs other than methotrexate. When used as monotherapy, the dose of 40 mg subcutaneous every week may be administered in case of effect loss. Published studies indicate that adalimumab can be effective and safe in RA patients (Furst 2003, Weinblatt 2003).

OBJECTIVES

The aim of this review is to assess the efficacy and safety of adalimumab in the treatment of RA. Efficacy was defined in terms of clinical response according to the American College of Rheumatology (ACR) criteria (ACR 20/50/70) and the European League Against Rheumatism (EULAR) criteria, and in terms of radiographic progression defined by the Sharp, modified Sharp or Larsen methods. Safety was defined by the frequency of adverse events, serious adverse events, and withdrawals due to adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) or controlled clinical trials (CCTs) comparing adalimumab alone or in combination with DMARDs to placebo or other DMARDs.

Types of participants

Patients with confirmed RA according to the American College of Rheumatology 1987 revised criteria (Arnett 1988), who had active disease as defined in every study. Patients who have failed methotrexate or other DMARDs therapy, and, also, DMARDs naive patients might be included.

Types of interventions

Adalimumab 20, 40, 80 mg sc every week to every-other week, alone or in combination with DMARDs versus placebo or DMARDs.

Types of outcome measures

The primary outcome was the response rate to treatment with adalimumab as defined by the American College of Rheumatology (ACR) (Felson 1995) and the European League Against Rheumatism (EULAR) criteria (Van Gestel 1996). The variables included in these definitions that are reported in this review are: tender joint count; swollen joint count; patient's assessment of global pain on a 0 to 100 visual analogue scale (VAS) or categorical scale; patient and physician assessment of disease activity on a VAS or categorical scale; patient assessment of functional ability as measured by the Health Assessment Questionnaire (HAQ); and laboratory parameters (i.e., acute phase reactants, such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

An ACR20/50/70 response is defined as a 20/50/70 per cent improvement in tender and swollen joints counts and the same level of improvement in three of the five following variables: patient and physician global assessments, pain, HAQ, and acute phase reactants.

The EULAR criteria defines response (good, moderate and none) according to certain cut-offs for both the absolute values and relative changes in the Disease Activity Score (DAS) (van der Heijde 1993). The DAS is a composite index that is computed by means of solving a linear equation for the combination of the values of tender and swollen joints counts, patient's global assessment of disease activity, and ESR value. When a twenty-eight joint count is used the index is reported as DAS 28. A good response is defined as a decrease in the DAS or DAS 28 > 1.2 from baseline with a final DAS < 2.4 (or DAS 28 < 3.2). None response is defined as a decrease in DAS or DAS 28 < 0.6 or a decrease > 0.6 and < 1.2 with a final DAS > 3.7 (or DAS 28 > 5.1). Any other scores are regarded as moderate response (Van Gestel 1996).

Radiographic progression, as measured by the Sharp, modified Sharp or Larsen methods, were also considered as a primary outcome for studies with available data. Health-related quality of life as measured by the SF-36 or other instruments were considered as a secondary outcome for studies with available data. Safety outcomes included adverse events, serious adverse events and withdrawals due to adverse events.

Search methods for identification of studies

The following electronic databases were searched up to August, 2004: MEDLINE, CINAHL, EBM Reviews (CDSR, ACP Journal Club, DARE and CENTRAL) and HealthSTAR. Adalimumab was searched as a text word as it is not currently indexed. The search was not limited by language, year of publication or type of publication. The specific search strategy is shown below. In addition, the proceedings of major rheumatology conferences including The American College of Rheumatology (ACR) and the European League of Rheumatology (EULAR) were hand searched. The reference lists from comprehensive reviews and identified clinical trials were also searched. Content experts and the pharmaceutical companies that manufacture adalimumab were contacted to obtain additional unpublished data from published trials.

Search Strategy:

1 exp arthritis, rheumatoid/ or *arthritis, juvenile rheumatoid/ or *caplan's syndrome/ or *felty's syndrome/ or *rheumatoid nodule/

*sjogren's syndrome/ or *spondylitis, ankylosing/ or *still's disease, adult-onset/

2 (felty\$ adj2 syndrome).tw.

3 (caplan\$ adj2 syndrome).tw.

4 rheumatoid nodule.tw.

5 (sjogren\$ adj2 syndrome).tw.

6 (sicca adj2 syndrome).tw.

7 still\$ disease.tw.

8 (spondylitis adj2 ankylosing).tw.

9 (arthritis adj2 rheumat\$).tw.

10 or/1-9

11 adalimumab.tw.

12 humira.tw.

13 anti-interleukin\$.tw.

14 anti-tumour necrosis factor\$.tw.

15 anti-tumour necrosis factor.tw.

16 anti-tnf.tw.

17 *Tumour Necrosis Factor/

18 *Antibodies, Monoclonal/tu [Therapeutic Use]

19 or/11-18

20 10 and 19

Data collection and analysis

SELECTION OF TRIALS

In a first step, two reviewers (FNS and IVT) independently selected the trials based on title and abstract. They assessed whether the studies met the inclusion criteria. Of the selected references, the full article was retrieved for final assessment. In a second step, two other reviewers independently performed a selection of the trials to be included in the review, using a standardized form (RAA and BHC). Disagreements on inclusion were resolved by discussion. METHODOLOGICAL QUALITY ASSESSMENT

The methodological quality was assessed by two reviewers independently (RAA and BHC). Disagreements were solved by consensus. When the disagreement persisted, a third reviewer made the final decision (IVT). The reviewers considered a set of methodological criteria, including: quality of allocation procedures, blinding, description of interventions and outcome measures, and description and statistical management of withdrawals and losses to follow up. The criteria list is based on the recommendations from the Cochrane Musculoskeletal Injuries Group and a Delphi list (Clarke 2001, Verhagen 1998). The following criteria were coded as A (clearly yes), B (not sure) or C (clearly no):

- -Was the assigned treatment adequately concealed prior to allocation?
- -Was randomisation performed? Was the method described?
- -Were the treatment and control groups comparable at entry?
- -Were the outcome assessors blinded to treatment status?
- -Were the subjects blinded to assignment status after allocation?
- -Were the interventions clearly defined?
- -Were the outcome measures clearly defined?
- -Were the outcomes of patients who withdrew described and included in the analysis (intention to treat)?

A global quality level was estimated for each study according these criteria (Clarke 2001):

- -Level A (low risk of bias): all of the individual criteria met (all of them scored A).
- -Level B (moderate risk of bias): one or more individual criteria partially met (one or more individual criteria scored B).
- -Level C (high risk of bias): one or more individual criteria not met (one or more criteria scored C).

Jadad scale (Jadad 1996) was also used for assessing the methodological quality of the studies. It contains five questions about the type of the study (randomized and double-blinded), the description of the withdrawals and loss of follow up, and the quality of the randomization and blindness. The Jadad scale goes from 0 to 5 and scores of 3 or higher mean a good methodological quality. GRADING OF EVIDENCE

We used the grading system described in the 2004 book Evidencebased Rheumatology (Tugwell 2004) and recommended by the Musculoskeletal Group:

Platinum: A published systematic review that has at least two individual controlled trials each satisfying the following:

- ·Sample sizes of at least 50 per group if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.
- ·Blinding of patients and assessors for outcomes.
- ·Handling of withdrawals >80% follow up (imputations based on

methods such as Last Observation Carried Forward (LOCF) are acceptable).

·Concealment of treatment allocation.

Gold: At least one randomised clinical trial meeting all of the following criteria for the major outcome(s) as reported:

- ·Sample sizes of at least 50 per group if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.
- ·Blinding of patients and assessors for outcomes.
- \cdot Handling of withdrawals > 80% follow up (imputations based on methods such as LOCF are acceptable).
- ·Concealment of treatment allocation.

Silver: A systematic review or randomised trial that does not meet the above criteria. Silver ranking would also include evidence from at least one study of non-randomised cohorts that did and did not receive the therapy, or evidence from at least one high quality casecontrol study. A randomised trial with a 'head-to-head' comparison of agents would be considered silver level ranking unless a reference were provided to a comparison of one of the agents to placebo showing at least a 20% relative difference.

Bronze: The bronze ranking is given to evidence if at least one high quality case series without controls (including simple before/ after studies in which patients act as their own control) or if the conclusion is derived from expert opinion based on clinical experience without reference to any of the foregoing (for example, argument from physiology, bench research or first principles).

DATA EXTRACTION

Two reviewers independently extracted the data using a standardized form (RAA and BHC). For each trial, information regarding study design, characteristics of the population, interventions, and outcome measures were collected. Information about previous and/or concomitant use of DMARDs, use and dose of steroids, and disease duration was also collected.

ANALYSIS

The data were analysed using an intention to treat model. Continuous data were analysed as a weighted mean difference or standardized mean difference for outcome measures ascertained with different tools. Dichotomous data are reported as relative risk and number needed to treat (NNT) estimated. A chi square test with n-1 degrees of freedom was performed in order to assess the homogeneity of the data. A p level < 0.05 was considered significant. The data were pooled using a random effect model if the studies were homogeneous. Although fixed effects model is commonly used if there is no heterogeneity, a random effects model was preferred in this review because it yields a more conservative estimation of the results with larger confidence intervals. If significant heterogeneity was found (p<0.05 by chi-square test), the data were not pooled. In this case, the potential factors underlying this phenomenon, including differences in methodological quality, were considered and summarized. The mean and the standard deviation were used when available.

CLINICAL RELEVANCE TABLES

Clinical relevance tables were compiled under additional tables to improve the readability of the review. For dichotomous outcomes, like complications, the NNTs were calculated from the control group event rate and the relative risk using the Visual Rx NNT calculator (Cates 2003). For beneficial events, odds ratio was used for calculating NNTs because the method using relative risk gives incorrect answers. The baseline risk was entered directly from the pooled observed events in the control group displayed on the RevMan Metaview screen. The pooled control event rate (expressed as a percentage) was used. It is the sum of all the events in the control groups (in all trials) divided by the total patient numbers in control groups in all trials. The NNTs in individual studies were calculating as one absolute risk difference. Continuous outcome tables are also presented under additional tables. Absolute benefit was calculated as the improvement in the intervention group minus the improvement in the control group, in the original units. Relative difference in the change from baseline was calculated as the absolute benefit divided by the baseline mean of the control group.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Furst 2003 was a multicenter, randomised, double-blind, 24weeks, placebo-controlled study comparing adalimumab sc 40 mg every other week versus placebo. RA patients (ACR criteria), with active disease (at least nine tender and six swollen joints) were included. DMARDs were allowed if stable doses in the previous twenty-eight days. The main outcome was safety but efficacy data (ACR response) were provided. The included patients had a mean RA duration of 9.3, and 11.5 years in the two arms of the study, respectively. The mean number of previous DMARDs ranged from zero to four. In the adalimumab group 8.2% of the patients had not used previous DMARDs, 34.6% had used one DMARD, 25.5% two DMARDs, 16.4% three of them, and 15.4% four previous DMARDs. In placebo group 7.2% of the patients had not used previous DMARDs, 32.7% had used one previous DMARD, 24.2% two DMARDs, 17.9% three of them, and 17.9% four previous DMARDs. At baseline, the mean tender joint count was 27.3, and 27.6 in the two arms of the study, respectively; the mean swollen joint count was 20.9, and 21.3; and the mean HAQ was 1.5 in both, adalimumab and placebo groups.

Keystone 2004 was a multicenter, randomised, double-blind, 52-weeks, placebo-controlled study comparing adalimumab sc 40 mg every other week, 20 mg every week or placebo. RA patients (ACR criteria), with active disease (at least, nine tender and six swollen joints and CRP>1 mg/dl), positive rheumatoid factor, and, at least,

one radiological erosion in hands or feet, were included. Patients were required to have been on methotrexate therapy for, at least, three months at a stable dose of 12.5-25 mg/week for four weeks. DMARDs other than methotrexate were discontinued twenty-eight days before the study. Outcomes included ACR response, tender and swollen joints counts, patient pain assessments, patient and physician global assessments, CRP, HAQ, SF-36, and radiological indexes (modified Sharp index and erosion and space scores). The included patients had a mean RA duration of 11 years and they had used a mean of 2.4 previous DMARDs. At baseline, the mean tender joint count was of 27.3, 27.9, and 28.1 in the three arms of the study, respectively; the mean swollen joint count was of 19.3, 19.6, and 19.0; and the mean HAQ was 1.45, 1.44, and 1.48.

Rau 2004 was a multicenter, randomised, double-blind, placebocontrolled study comparing adalimumab sc or iv 1 mg/kg versus placebo. RA patients (ACR criteria), with active disease (DAS>3.2) and being treated with methotrexate were included. Patients received two double-blind doses of randomised study medication. The second injection was given as earlier four weeks after the first injection to patients with a loss or absence of a moderate EULAR response. Patients with EULAR response received the second injection three months after the first dose. All patients continued treatment with stable doses of methotrexate (7.5-25 mg/week). Outcomes were EULAR and ACR responses, DAS, Ritchie joint index, swollen joints count, patient pain assessment, patient and physician global assessments, HAQ, ESR, and CRP. The included patients had a mean RA duration of 10.6, and 11.5 years in the Adalimumab sc and placebo group, respectively. The mean number of previous DMARDs was 3.5, and 3.3. At baseline, the mean tender joint count was 15.5, and 17.6; the swollen joint count was 19.5, and 18.8; and the mean HAQ was 1.33, and 1.38

Van de Putte 2003 was a multicenter, randomised, double-blind, 12-weeks, placebo-controlled study comparing adalimumab sc 20, 40, or 80 mg every week versus placebo. RA patients (ACR criteria), with active disease (at least, twelve tender and ten swollen joints, ESR>28 mm, and CRP>20 mg/L), who had failed to one or more DMARDs were included. DMARDs were discontinued four weeks before the start of the study. At week 12, patients in the placebo group were switched to adalimumab 40 mg and the blinded study continued until week 40. Main outcomes were ACR response, tender and swollen joints count, patient pain assessment, patient and physician global assessments, HAQ, ESR, CRP, and DAS28. The included patients had a mean RA duration of 10 years. The mean number of previous DMARDs was 3.75. At baseline, the mean tender joint count was 31.5, the mean swollen joint count was 19.5, the mean DAS28 was 7.0, and the mean HAQ was 1.71.

Van de Putte 2004, was a multicenter, randomised, double-blind, 26-week, placebo-controlled study comparing adalimumab sc 20 mg every or every other week, 40 mg every or every other week versus placebo. It was not the same study as Van de Putte 2003.

RA patients (ACR criteria), with active disease (at least, twelve tender and ten swollen joints, ESR>28 mm, and CRP>20 mg/L), who had failed to one or more previous DMARDs, were included. DMARDs were discontinued four weeks before the start of the study. Main outcomes were ACR and EULAR responses, tender and swollen joints counts, patient pain assessment, patient and physician global assessments, ESR, CRP, HAQ, and DAS28. The included patients had a mean RA duration of 11.3, 9.3, 11.9, 10.6, and 11.6 years in the five arms of the study, respectively. The mean number of previous DMARDs was 3.6, 3.7, 3.8, 3.8, and 3.6. At baseline, the mean tender joint count was 35.3, 33.9, 33.8, 33.7, and 35.5 in the five arms of the study, respectively; the mean swollen joint count was 19.8, 19.6, 19.3, 20.5, and 19.8; the mean DAS28 was 7.09, 7.08, 7.02, 7.07, 7.09; and the mean HAQ was 1.88, 1.88, 1.84,1.83, and 1.88.

Weinblatt 2003 was a multicenter, randomised, double-blind, 24weeks, placebo-controlled study comparing adalimumab sc 20, 40, or 80 mg every other week versus placebo. RA patients (ACR criteria), with active disease (at least, nine tender and six swollen joints), were included. All patients had been treated with methotrexate for a minimum of six months and were on a stable dose (12.5-25 mg/ week) at least four weeks before entering the study. All of them had failed to one or more DMARDs besides methotrexate, but no more than four DMARDs. The treatment with methotrexate was continued during the study but other DMARDs were discontinued four week before the start of the study. Main outcomes included ACR response, tender and swollen joints counts, patient pain assessment, patient and physician global assessments, HAQ, CRP, and SF-36. The included patients had a mean RA duration of 13.1, 12.2, 12.8, and 11.1 years in the four arms of the study, respectively. They had used a mean of 3 previous DMARDs. At baseline, the mean tender joint count was 28.5, 28.0, 30.3, and 28.7, respectively; the mean swollen joint count was 17.6, 17.3, 17.0, and 16.9; and the mean HAQ was 1.52, 1.55, 1.55, and 1.64.

Risk of bias in included studies

Furst 2003, Keystone 2004, Rau 2004, and Van de Putte 2003 had a global quality level (as described in the "Methods" section) rated as B, because the procedures of randomisation and blinding were not described, and allocation concealment was not clear. The Jadad scale was scored as 3. Van de Putte 2004 had a global quality level rated as A, and the Jadad scale was scored as 5. Weinblatt 2003 had a global quality level rated as A. Blinding procedure was not described and the randomisation wad done using blocks of 8. It can be accepted that randomisation was a central procedure and there was allocation concealment . The Jadad scale was scored as

Effects of interventions

Six studies with 2,390 patients were included in this review: Furst 2003, Keystone 2004, Rau 2004, Van de Putte 2003, Van de Putte 2004, and Weinblatt 2003. All of them were published studies and used intention to treat analysis. Their characteristics have been described above and summarized in the table of included studies. Three of these studies (Rau 2004, Van de Putte 2003, and Van de Putte 2004) were continued with an open-label phase but the data of these open extensions were not included in the analysis. Abbott Immunology, the manufacturer of adalimumab, was contacted but unpublished data were not provided. The excluded studies (Barrera 2002, Den Broeder 2002a, Den Broeder 2002b, Den Broeder 2002c, Den Broeder 2003, Keystone 2003, Schatenkirchner 1998, Tjioe 2003, Velagapudi 2004, and Weisman 2003) and the reasons for their exclusion are summarized in the table of excluded studies. All results are reported using a random effect model. As the scales used for continuous variables were the same in the studies, continuous data are reported as weighted mean difference (WMD) with 95% confidence interval (95%CI), absolute benefit (AB) and relative difference(RD). Dichotomous outcomes are reported as relative risk (RR) with 95% CI, absolute risk difference (ARD) or risk difference (RDiff) with 95%CI and number needed to treat (NNT) or to harm (NNH).

Two comparisons were done: A. Adalimumab sc+ methotrexate (or DMARDs) versus placebo sc+ methotrexate (or DMARDs). B. Adalimumab sc in monotherapy versus placebo sc. The results on ACR and/or EULAR responses, DAS28, radiographic progression, and safety are described with detail in the text. The results with the approved dose of adalimumab (40 mg every other week) are also described with detail in the text. In order to improve the readability of the text of the review, other results (about components of the ACR response) with other administration schedules are only reported in the graphs and tables.

A. ADALIMUMAB + METHOTREXATE (OR DMARDs) versus PLACEBO + METHOTREXATE (OR DMARDs).

Four studies were included in this comparison: Furst 2003, Keystone 2004, Rau 2004, and Weinblatt 2003. Efficacy data were available at 24 and 52 weeks. In addition, Weinblatt 2003 reported ACR 20 response at week 16 and Rau 2004 reported data on a four-week period after the first injection of adalimumab. The relative risk (95%CI) for achieving an ACR 20 response at week 16 was 2.49 (1.46-4.24) with adalimumab 20 mg every other week (e.o.w.), 3.35 (2.01-5.56) with 40 mg e.o.w., and 2.94 (1.75-4.93) with 80 mg e.o. w. The relative risk (95%CI) for achieving an ACR 20 response in a four-week period after an injection of adalimumab 1 mg/kg was 2.40 (1.06-5.41).

A.1. EFFICACY AT 24 WEEKS

A.1.1. ADALIMUMAB 20 mg EVERY WEEK (e.w.).

Only one study (Keystone 2004) was available.

ACR RESPONSE.

60.8% of the patients on adalimumab achieved an ACR 20 response versus 29.5% of those in the placebo group with an absolute risk difference of 31.3%, in terms of risk difference 0.31 (95%CI 0.22-0.40). The relative risk (95%CI) was 2.06 (1.62-2.62) with a number needed to treat of 3.2.

ACR 50 response was achieved by 41.03% of the patients on adalimumab versus 9.5% of the patients on placebo with an absolute risk difference of 31.53% (risk difference 0.32, 95%CI 0.24-0.39). The relative risk (95%CI) was 4.32 (2.73-6.82) with a number needed to treat of 3.2.

ACR 70 was achieved by 17.45% of the patients on adalimumab versus 2.5% of those on placebo with an absolute risk difference of 14.95% (risk difference 0.15, 95%CI 0.09-0.21). The relative risk (95%CI) was 6.98 (2.80-17.41) with a number needed to treat of 6.7.

EVIDENCE LEVEL: SILVER

A.1.2. ADALIMUMAB 20 mg EVERY OTHER WEEK (e.o.w.).

Only one study (Weinblatt 2003) was available.

ACR RESPONSE

ACR 20 response was achieved by 47.82% of the patients in the adalimumab group versus 14.51% of those in the placebo group with an absolute risk difference of 33.31% (risk difference 0.33, 95%CI 0.19-0.48). The relative risk (95%CI) was 3.29 (1.72-6.33) with a number needed to treat of 3.0.

ACR 50 response was achieved by 31.88% of the adalimumab patients versus 8.06% of the placebo patients with an absolute risk difference of 23.82% (risk difference 0.24, 95%CI 0.11-0.37). The relative risk (95%CI) was 3.95 (1.59-9.81) with a number needed to treat of 4.2.

ACR 70 response was achieved by 10.14% of the patients in the adalimumab group versus 4.83% of those in the placebo group with an absolute risk difference of 5.31% (risk difference 0.05, 95%CI -0.04-0.14). The relative risk (95%CI) was 2.10 (0.57-7.76) with a number needed to treat of 18.8.

EVIDENCE LEVEL: GOLD

A.1.3. ADALIMUMAB 40 mg e.o.w.

Data from three studies (Furst 2003, Keystone 2004, Weinblatt 2003) were available.

ACR RESPONSE

In Furst 2003, ACR 20 response was achieved by 53.63% of the adalimumab patients versus 35.18% of the placebo patients with an absolute risk difference of 18.45% (risk difference 0.18, 95%CI 0.10-0.27). The relative risk (95%CI) was 1.52 (1.25-1.86) with a number needed to treat of 5.4. In Weinblatt 2003, ACR 20 response was achieved by 67.16% of the adalimumab patients versus 14.5% of the placebo patients with an absolute risk difference of 52.66% (risk difference 0.53, 95%CI 0.38-0.67). The relative risk (95%CI) was 4.63 (2.47-8.66) with a number needed to treat of 1.9. In Keystone 2004, ACR 20 response was achieved by 63.28% of the adalimumab patients versus 29.5% of the placebo patients

with an absolute risk difference of 33.78% (risk difference 0.34, 95%CI 0.25-0.43). The relative risk (95%CI) was 2.15 (1.69-2.72) with a number needed to treat of 3.0. Significant heterogeneity (chi square 13.73, df= 2, p=0.001) was observed. Although the analysis programme RevMan automatically pooled the results (as the graph shows), the pooled results were not considered due to the significant heterogeneity.

In Furst 2003, ACR 50 response was achieved in 29.50% of the adalimumab patients versus 11.85% of the placebo patients with an absolute risk difference of 17.65% (risk difference 0.18, 95%CI 0.11-0.24). The relative risk (95%CI) was 2.49 (1.71-3.62) with a number needed to treat of 5.7. In Weinblatt 2003, ACR 50 response was achieved by 55.22% of the adalimumab patients versus 8.06% of the placebo patients with an absolute risk difference of 47.16% (risk difference 0.47, 95%CI 0.33-0.61). The relative risk (95%CI) was 6.85 (2.88-16.31) with a number needed to treat of 2.1. In Keystone 2004, ACR 50 response was achieved by 39.13% of the adalimumab patients versus 9.5% of the placebo patients with an absolute risk difference of 29.63% (risk difference 0.30, 95%CI 0.22-0.37). The relative risk (95%CI) was 4.12 (2.60-6.53) with a number needed to treat of 3.4. The test for heterogeneity showed chi square= 5.88, df= 2, p=0.05. Data from the three studies including 1067 patients were pooled. ACR 50 response was achieved by 36.44% of the adalimumab patients versus 10.52% of the placebo patients with a weighted risk difference (95%CI) of 0.30 (0.16-0.45). The relative risk (95%CI) was 3.73 (2.21-6.29) with a number needed to treat (95%CI) of 4.0 (3.0-8.0). When considered Keystone 2004 and Weinblatt 2003, significant heterogeneity was not found. With those studies, an ACR 50 response was achieved by 43.06% of the adalimumab patients versus 9.16% of the placebo patients with a weighted risk difference (95%CI) of 0.37 (0.20-0.55). The relative risk (95%CI) was 4.63 (3.04-7.05) with a number needed to treat (95%CI) of 3.0 (2.0-6.0).

In Furst 2003, ACR 70 response was achieved by 14.17% of the adalimumab patients versus 3.70% of the placebo patients with an absolute risk difference of 10.47% (risk difference 0.10, 95%CI 0.06-0.15). The relative risk (95%CI) was 3.83 (1.94-7.54) with a number needed to treat of 9.6. In Weinblatt 2003, ACR 70 response was achieved by 26.86% of the adalimumab patients versus 4.83% of the placebo patients with an absolute risk difference of 22.03% (risk difference 0.22, 95%CI 0.10-0.34). The relative risk (95%CI) was 5.55 (1.72-17.93) with a number needed to treat of 4.5. In Keystone 2004, ACR 70 response was achieved by 20.77% of the adalimumab patients versus 2.5% of the placebo patients with an absolute risk difference of 18.27% (risk difference 0.18, 95%CI 0.12-0.24). The relative risk (95%CI) was 8.31 (3.36-20.55) with a number needed to treat of 5.5. As significant heterogeneity was not found, data from the three studies including 1067 patients were pooled. ACR 70 response was achieved by 18.31% of the adalimumab patients versus 3.38% of the placebo patients. The weighted risk difference (95%CI) was 0.16 (0.09-0.23). The

relative risk (95%CI) was 5.14 (3.14-8.41) with a number needed to treat (95%CI) of 7.0 (5.0-13.0).

COMPONENTS OF ACR RESPONSE

Data about other outcomes measures were only available in Weinblatt 2003, and Keystone 2004, including 536 patients.

Tender joints (TJ)

In Weinblatt 2003, reduction in the number of TJ was -14.40 (18.40) in the patients treated with adalimumab versus -5.30 (12.10) in those treated with placebo with an absolute benefit of -9.10 and a relative difference of 31.7%. The weighed mean difference (95%CI) was -9.10 (-14.44 to -3.76). In Keystone 2004, the reduction in the number of TJ was -15.40 (12.30) in the adalimumab patients versus -9.30 (14.40) in the placebo patients with an absolute benefit of -6.10 and a relative difference of 21.7%. The weighed mean difference (95%CI) was -6.10 (-8.71 to -3.49). The pooled weighed mean difference (95%CI) was -6.68 (-9.02 to -4.34).

Swollen joint (SJ)

In Weinblatt 2003, the reduction in the number of SJ was -10.40 (10.00) in the adalimumab patients versus -2.90 (10.50) in the placebo patients with an absolute benefit of -7.5 and a relative difference of 44.37%. The weighed mean difference (95%CI) was -7.50 (-11.04 to -3.96). In Keystone 2004, reduction in the number of SJ was -11.10 (9.70) in the adalimumab patients versus -5.90 (10.60) in the placebo patients with an absolute benefit of -5.20 and a relative difference of 27.36%. The WMD (95%CI) was -5.20 (-7.18 to -3.22). The pooled weighed mean difference (95%CI) was -5.86 (-7.90 to -3.82).

Patient pain assessment (PPA)

In Weinblatt 2003, reduction in the PPA was -25.10 (33.10) in the adalimumab patients versus -8.60 (22.50) in the placebo patients with an absolute benefit of -16.50 and a relative difference of 28.84%. The weighed mean difference (95%CI) was -16.50 (-26.20 to -6.80). In Keystone 2004, reduction in the PPA was -28.20 (25.80) in the adalimumab patients versus -12.60 (26.10) in the placebo patients with an absolute benefit of -15.60 and a relative difference of 27.71%. The weighed mean difference (95%CI) was -15.60 (-20.64 to -10.56). The pooled weighed mean difference (95%CI) was -15.79 (-20.27 to -11.32).

Patient global assessment (PGA)

In Weinblatt 2003, reduction in the PGA was -29.70 (31.80) in the adalimumab patients versus -8.60 (25.10) in the placebo patients with an absolute benefit of -21.10 and a relative difference of 36.37%. The weighed mean difference (95%CI) was -21.10 (-30.95 to -11.25). In Keystone 2004, reduction in the PGA was -27.20 (26.90) in the adalimumab patients versus -11.40 (28.10) in the placebo patients with an absolute benefit of -15.80 and a relative difference of 29.1%. The weighed mean difference (95%CI) was -15.80 (-21.15 to -10.45). The pooled weighed mean difference (95%CI) was -17.01 (-21.71 to -12.31).

Physician global assessment (PhyGA)

In Weinblatt 2003, reduction in the PhyGA was -31.10 (24.90) in the adalimumab patients versus -6.80 (24.50) in the placebo patients with an absolute benefit of -24.30 and a relative difference of 41.25%. The weighed mean difference (95%CI) was -24.30 (-32.83 to -15.77). In Keystone 2004, reduction in the PhyGA was -37.30 (21.60) in the adalimumab patients versus -21.10 (25.30) in the placebo patients with an absolute benefit of -16.20 and a RD of 26.42%. The weighed mean difference (95%CI) was -16.20 (-20.78 to -11.62). The pooled weighed mean difference (95%CI) was -19.42 (-27.19 to -11.65).

Health assessment questionnaire (HAQ)

In Weinblatt 2003, reduction in the HAQ score was -0.62 (0.63) in the adalimumab patients versus -0.27 (0.57) in the placebo patients with an absolute benefit of -0.35 and a relative difference of 21.34%. The weighed mean difference (95%CI) was -0.35 (-0.56 to -0.14). In Keystone 2004, reduction in the HAQ score was -0.56 (0.52) in the adalimumab patients versus -0.24 (0.52) in the placebo patients with an absolute benefit of -0.32 and a relative difference of 21.62%. The weighed mean difference (95%CI) was -0.32 (-0.42 to -0.22). The pooled weighed mean difference (95%CI) was -0.33 (-0.42 to -0.23).

C reactive Protein (CRP)

In Weinblatt 2003, reduction in the CRP values was -1.60 (1.60) in the adalimumab patients versus 0.10 (2.40) in the placebo patients with an absolute benefit of -1.70 and a relative difference of 54.83%. The weighed mean difference (95%CI) was -1.70 (-2.41 to -0.99). In Keystone 2004, reduction in the CRP values was -1.00 (2.90) in the adalimumab patients versus -0.20 (1.90) in the placebo patients with an absolute benefit of -0.80 and a relative difference of 44.44%. The weighed mean difference (95%CI) was -0.80 (-1.27 to -0.33). The test for heterogeneity showed chi square= 4.27, df= 2, p= 0.04. Data were pooled. The weighed mean difference (95%CI) was -1.21 (-2.09 to -0.33).

EVIDENCE LEVEL: GOLD

A.1.4. ADALIMUMAB 80 mg e.o.w.

Data from one only study (Weinblatt 2003) were available.

ACR RESPONSE

ACR 20 response was achieved by 65.75% of the patients in the adalimumab group versus 14.51% of those in the placebo group with an absolute risk difference of 51.24% (risk difference 0.51, 95%CI 0.37-0.65). The relative risk (95%CI) was 4.53 (2.42-8.47) with a number needed to treat of 1.9.

ACR 50 response was achieved by 42.46% of the adalimumab treated patients versus 8.06% of the placebo treated patients with an absolute risk difference of 34.4% (risk difference 0.34, 95%CI 0.21-0.48). The relative risk (95%CI) was 5.27 (2.18-12.72) with a number needed to treat of 2.9.

ACR 70 response was achieved by 19.17% of the adalimumab patients versus 4.83% of the placebo patients with an absolute risk difference of 14.34% (risk difference 0.14, 95%CI 0.04-0.25).

The relative risk (95%CI) was 3.96 (1.19-13.16) with a number needed to treat of 7.0.

EVIDENCE LEVEL: GOLD A.2. EFFICACY AT 52 WEEKS

Efficacy data at 52 weeks were available in only one study (Keystone 2004).

A.2.1. ADALIMUMAB 20 mg e.w. ACR RESPONSE

ACR 20 response was achieved by 54.71% of the adalimumab patients versus 24% of the placebo patients with an absolute risk difference of 30.71% (risk difference 0.31, 95%CI 0.22-0.40). The relative risk (95%CI) was 2.28 (1.73-3.00) with a number needed to treat of 3.2.

ACR 50 response was achieved by 37.73% of the adalimumab patients versus 9.5% of the placebo patients with an absolute risk difference of 28.23% (risk difference 0.28, 95% 0.21-0.36). The relative risk (95%CI) was 3.97 (2.50-6.30) with a number needed to treat of 3.5.

ACR 70 response was achieved by 20.75% of the adalimumab patients versus 4.5% of the placebo patients with an absolute risk difference of 16.25% (risk difference 0.16, 95%CI 0.10-0.22). The relative risk (95%CI) was 4.61 (2.31-9.20) with a number needed to treat of 6.1.

RADIOLOGICAL OUTCOMES

The change in the modified Sharp index was 0.80 (4.90) in the adalimumab patients versus 2.70 (6.80) in the placebo patients with an absolute benefit of -1.90 and a relative difference of 2.86%. The weighed mean difference (95%CI) was -1.90 (-3.13 to -0.67). The change in the erosion score was 0.40 (2.50) in the adalimumab patients versus 1.60 (4.40) in the placebo patients with an absolute benefit of -1.20 and a relative difference of 3.22%. The weighed mean difference (95%CI) was -1.20 (-1.94 to -0.46).

EVIDENCE LEVEL: SILVER

A.2.2. ADALIMUMAB 40 mg e.o.w.

Data from one only study (Keystone 2004) were available.

ACR RESPONSE

ACR 20 response was achieved by 58.93% of the adalimumab patients versus 24% of the placebo patients with an absolute risk difference of 34.93% (risk difference 0.35, 95%CI 0.26-0.44). The relative risk (95%CI) was 2.46 (1.87-3.22) with a number needed to treat of 2.9.

ACR 50 response was achieved by 41.54% of the adalimumab patients versus 9.5% of the placebo patients with an absolute risk difference of 32.04% (risk difference 0.32, 95%CI 0.24-0.40). The relative risk (95%CI) was 4.37 (2.77-6.91) with a number needed to treat of 3.1.

ACR 70 response was achieved by 23.18% of the adalimumab patients versus 4.5% of the placebo patients with an absolute risk

difference of 18.68% (risk difference 0.19, 95%CI 0.12-0.25). The relative risk (95%CI) was 5.15 (2.60-10.22) with a number needed to treat of 5.3.

COMPONENTS OF ACR RESPONSE

Tender Joints (TJ)

Mean change (SD) in the number of TJ was -16.60 (12.80) in the adalimumab patients versus -9.60 (14.70) in the placebo patients with an absolute benefit of -7.00 and a relative difference of 24.9%. The weighed mean difference (95%CI) was -7.00 (-9.68 to -4.32).

Swollen Joints (SJ)

Mean change (SD) in the number of SJ was -11.90 (11.00) in the adalimumab patients versus -5.60 (10.30) in the placebo patients with an absolute benefit of -6.30 and a relative difference of 33.15%. The weighed mean difference (95%CI) was -6.30 (-8.37 to -4.23).

Patient Pain Assessment (PPA)

Mean change (SD) in the PPA was -29.40 (26.40) in the adalimumab patients versus -11.20 (27.70) in the placebo patients with an absolute benefit of -18.20 and a relative difference of 32.32%. The weighed mean difference (95%CI) was -18.20 (-23.46 to -12.94).

Patient Global Assessment (PGA)

Mean change (SD) in the PGA was -27.50 (28.40) in the adalimumab patients versus -10.90 (30.40) in he placebo patients with an absolute benefit of -16.60 and a relative difference of 30.57%. The weighed mean difference (95%CI) was -16.60 (-22.32 to -10.88).

Physician Global Assessment (PhyGA)

Mean change (SD) in the PhyGA was -39.40 (22.20) in the adalimumab patients versus -19.50 (25.80) in the placebo patients with an absolute benefit of -19.90 and a relative difference of 32.46%. The weighed mean difference (95%CI) was -19.90 (-24.58 to -15.22).

Health Assessment Questionnaire (HAQ)

Mean change (SD) in the HAQ score was -0.59 (0.57) in the adalimumab patients versus -0.25 (0.56) in the placebo patients with an absolute benefit of -0.34 and a relative difference of 22.97%. The weighed mean difference (95%CI) was -0.34 (-0.45 to -0.23).

C reactive protein (CRP)

Mean change (SD) in the CRP values was -0.70 (1.70) in the adalimumab patients versus -0.10 (1.90) in the placebo patients with an absolute benefit of -0.60 and a relative difference of 33.33%. The weighed mean difference (95% CI) was -0.60 (-0.93 to -0.27).

RADIOLOGICAL OUTCOMES

The available data included 355 patients.

The change in the modified Sharp Index was 0.10 (4.80) in the adalimumab patients versus 2.70 (6.80) in the placebo patients with an absolute benefit of -2.60 and a relative difference of 3.91%. The weighed mean difference (95%CI) was -2.60 (-3.83 to -1.37). The change in the erosion score was 0.00 (2.80) in the adalimumab patients versus 1.60 (4.40) in the placebo patients with an absolute benefit of -1.60 and a relative difference of 4.30%. The weighed

mean difference (95%CI) was -1.60 (-2.37 to -0.83).

The change in the joint space index was 0.10 (2.30) in the adalimumab patients versus 1.00 (3.00) in the placebo patients with an absolute benefit of -0.90 and a relative difference of 3.08%. The weighed mean difference (95%CI) was -0.90 (-1.46 to -0.34).

EVIDENCE LEVEL: SILVER

A.3. SAFETY

Data were analysed considering all doses of adalimumab and all periods of treatment. All of the included studies in this review were considered. Significant differences between adalimumab and placebo patients were only found in the rate of positive ANA and anti-DNA antibodies and in the frequency of serious infections. The results of the shorter and longer studies were homogeneous except in the rate of serious infections which were significantly more frequent in adalimumab patients in the longer study (Keystone 2004).

Adverse events (AEs)

There were not significant differences in the frequency of AEs between adalimumab and placebo groups in any of the studies with available data. These studies (Furst 2003, Keystone 2004, and Rau 2004) included 1186 patients. The rates of AEs were 87.73% in the adalimumab patients versus 84.07% in the control group (Furst 2003); 93.31% versus 90.5% (Keystone 2004); and 100% in both, adalimumab and placebo groups in Rau 2004. Pooled data were 91.40% in the adalimumab patients versus 87.29% in the placebo patients with relative risk (95%CI) of 1.04 (0.99-1.08). The most frequent AEs were upper respiratory tract infections, rhinitis, and headache.

Serious adverse events (SAEs)

SAEs were defined as those AEs life-threatening, requiring hospitalisation or leaving sequel (as defined by structural damage related to the adverse event). There were not significant differences in the frequency of SAEs between adalimumab and placebo groups in any of the studies with available data. These studies (Furst 2003; Rau 2004) included 567 patients. The rates of SAEs were 5.36% in the adalimumab patients versus 7.4% in the placebo patients (Furst 2003); and 5.55% in both, adalimumab and placebo groups, in Rau 2004. Pooled data were 5.37% in the adalimumab patients versus 7.29% in the placebo patients with a relative risk (95%CI) of 0.74 (0.39-1.40).

Withdrawals due to AEs

There were not significant differences in the frequency of withdrawals due to AEs between adalimumab and placebo groups in any of the studies with available data. These studies (Furst 2003, Keystone 2004, Rau 2004, and Weinblatt 2003) included 1457 patients. The rates of withdrawals due to AEs were 2.68% in the adalimumab patients versus 2.22% in the placebo patients (Furst 2003); 2.39% versus 3.22% (Weinblatt 2003); 10.02% versus 6.5% (Keystone 2004); and none in both, the adalimumab and placebo groups in Rau 2004. Pooled data were 5.95% in the adalimumab patients versus 3.81% in the placebo patients with a relative risk (95%CI) of 1.37 (0.83-2.25).

Infections

Data about global rate of infections were only available in Furst 2003. There were infections in 52.87% of the adalimumab patients versus 51.85% of the placebo patients with a relative risk (95%CI) of 1.02 (0.87-1.20).

Serious infections

The rates of serious infections were significantly heterogeneous, thus data were not pooled. In Furst 2003, serious infections were seen in 1.53% of the Adalimumab patients versus 2.22% of the placebo patients with a relative risk (95%CI) of 0.69 (0.20-2.42). In Rau 2004, none of the 36 patients had a serious infection. However, in the longer study (Keystone 2004, with data from 619 patients), 3.81% of the adalimumab patients had serious infections versus 0.5% of the placebo patients with an absolute risk difference of 3.31% (risk difference, 95%CI 0.03, 0.01-0.05). The relative risk (95%CI) was 7.64(1.02-57.18) with a number needed to harm (NNH) of 30.2.

Positive antinuclear antibodies (ANA)

Positive ANA were found in 26.5% of the adalimumab patients versus 15.23% of the placebo patients in Furst 2003 with an absolute risk difference of 11.27% (risk difference, 95%CI 0.11. 0.04-0.18), a relative risk (95%CI) of 1.74 (1.22-2.48) and a number needed to harm of 8.9. In the other studies the differences were not significant: 11.11% versus 6.12% in Weinblatt 2003, 12.09% versus 9.14% in Keystone 2004, and 5.55% in both groups in Rau 2004. Significant heterogeneity was not found, thus data from the three studies including 1335 patients were pooled. The global rates of positive ANA were 16.10% in the adalimumab patients versus 11.78% in the placebo patients with a weighted risk difference (95%CI) of 0.06 (0.01-0.10). The relative risk (95%CI) was 1.60 (1.20-2.13) with a number needed to harm (95%CI) of 15.0 (8.0-43.0).

Positive anti-DNA antibodies

Positive anti-DNA antibodies were found in 12.45% of the adalimumab patients versus 1% of the placebo patients in Furst 2003 with an absolute risk difference of 11.45% (risk difference, 95%CI 0.11, 0.07-0.15), a relative risk (95%CI) of 12.42 (3.87-39.87), and a number needed to harm of 8.7. In Weinblatt 2003 (3.92% versus 0%) and Keystone 2004 (11.66% versus 0%), the differences were not significant. Data from the three studies including 1022 patients were pooled. The global rates of positive anti-DNA antibodies were 9.46% in the adalimumab patients versus 0.73% in the placebo patients with a weighted risk difference (95%CI) of 0.09 (0.03-0.15). The relative risk (95%CI was 11.07 (4.05-30.31) with a number needed to harm (95%CI) of 14.0 (5.0-45.0).

Withdrawals

Data about the global rate of withdrawals in both groups, adalimumab and placebo, were available in Furst 2003, and Keystone 2004. There were not significant differences between adalimumab and placebo groups.

B. ADALIMUMAB versus PLACEBO

Efficacy data were available at weeks 2, 12, and 24/26. For the purpose of this review, weeks 24 and 26 were considered equivalents points along the time scale. Efficacy results at 2 weeks are only reported in the graphs. Efficacy data with adalimumab 40 mg e.o.w and 40 mg e.w. are reported with detail in the text.

B.1. EFFICACY AT 12 WEEKS

Data from only one study (Van de Putte 2003) were available.

B.1.1. ADALIMUMAB 20 mg e.w. ACR RESPONSE

An ACR 20 response was achieved by 50.7% of the adalimumab patients versus 10% of the placebo patients with an absolute risk difference of 40.7% (risk difference, 95% CI 0.41, 0.27-0.54). The relative risk (95%CI) was 5.07 (2.42-10.62) with a number needed to treat of 2.4.

An ACR 50 response was achieved by 23.94% of the adalimumab patients versus 1.42% of the placebo patients with an absolute risk difference of 22.52% (risk difference, 95% CI 0.23, 0.12-0.33). The relative risk (95%CI) was 16.76 (2.29-122.56) with a number needed to treat of 4.4.

An ACR 70 response was achieved by 11.26% of the adalimumab patients versus 0% of the placebo patients with an absolute risk difference of 11.26% (risk difference, 95% CI 0.11, 0.04-0.19). The relative risk (95%CI) was 16.76 (0.99-285.00) with a number needed to treat of 8.9.

DAS 28

Mean change (SD) of the DAS 28 was -1.80 (1.40) in the adalimumab patients versus -0.50 (1.10) in the placebo patients with an absolute benefit of -1.30 and a relative difference of 18.31%. The weighted mean difference (95%CI) was -1.30 (-1.71 to -0.88).

EVIDENCE LEVEL: SILVER

B.1.2. ADALIMUMAB 40 mg e.w.

ACR RESPONSE

An ACR 20 response was achieved by 57.14% of the adalimumab patients versus 10% of the placebo patients with an absolute risk difference of 47.14% (risk difference, 95%CI 0.47, 0.34-0.61). The relative risk (95%CI) was 5.71 (2.75-11.88) with a number needed to treat of 2.1.

An ACR 50 response was achieved by 27.14% of the adalimumab patients versus 1.42% of the placebo patients with an absolute risk difference of 25.72% (risk difference, 95%CI 0.26, 0.15-0.36). The relative risk (95%CI) was 19.00 (2.61-138.08) with a number needed to treat of 3.9.

An ACR 70 response was achieved by 10.00% of the adalimumab patients versus 0% of the placebo patients with an absolute risk difference of 10.00% (risk difference, 95%CI 0.10, 0.03-0.17). The relative risk (95%CI) was 15.00 (0.87-257.70) with a number needed to treat of 10.0.

DAS 28 AND COMPONENTS OF ACR RESPONSE DAS 28

Mean change (SD) of the DAS 28 was -2.10 (2.30) in the adali-

mumab patients versus -0.50 (1.10) in the placebo patients with an absolute benefit of -1.60 and relative difference of 22.53%. The weighted mean difference (95%CI) was -1.60 (-2.00 to -1.20).

Tender Joints (TJ)

Mean change (SD) of the TJ was -15.30 (11.60) in the adalimumab patients versus -5.10 (17.80) in the placebo patients with an absolute benefit of -10.20 and relative difference of 33.01%. The weighted mean difference (95%CI) was -10.20 (-15.18 to -5.22).

Swollen Joints (SJ)

Mean change (SD) of the SJ was -9.60 (7.10) in the adalimumab patients versus -2.80 (7.30) in the placebo patients with an absolute benefit of -6.80 and relative difference of 33.66%. The weighted mean difference (95%CI) was -6.80 (-9.19 to -4.41).

Patient Pain Assessment (PPA)

Mean change (SD) of the PPA was -35.30 (29.40) in the adalimumab patients versus -7.80 (26.90) in the placebo patients with an absolute benefit of -27.50 and relative difference of 37.98%. The weighted mean difference (95%CI) was -27.50 (-36.84 to -18.16).

Patient Global Assessment (PGA)

Mean change (SD) of the PGA was -37.60 (27.90) in the adalimumab patients versus -6.90 (26.00) in the placebo patients with an absolute benefit of -30.70 and relative difference of 41.76%. The weighted mean difference (95%CI) was -30.70 (-39.63 to -21.77).

Physician Global Assessment (PhyGA)

Mean change (SD) of the PhyGA was -35.70 (20.30) in the adalimumab patients versus -5.00 (22.00) in the placebo patients with an absolute benefit of -30.70 and relative difference of 46.94%. The weighted mean difference (95%CI) was -30.70 (-37.71 to -23.69)

Health Assessment Questionnaire (HAQ)

Mean change (SD) of the HAQ was -0.47 (0.43) in the adalimumab patients versus -0.04 (0.37) in the placebo patients with an absolute benefit of -0.43 and relative difference of 26.38%. The weighted mean difference (95%CI) was -0.43 (-0.56 to -0.30).

Erythrocyte Sedimentation Rate (ESR)

Mean change (SD) of the ESR was -17.90 (20.00) in the adalimumab patients versus -2.00 (20.10) in the placebo patients with an absolute benefit of -15.90 and relative difference of 29.66%. The weighted mean difference (95%CI) was -15.90 (-22.54 to -9.26).

C reactive protein (CRP)

Mean change (SD) of the CRP was -32.00 (3.40) in the adalimumab patients versus -1.00 (3.40) in the placebo patients with an absolute benefit of -31.00 and relative difference of 49.20%. The weighted mean difference (95%CI) was -31.00 (-32.13 to -29.87).

EVIDENCE LEVEL: SILVER
B.1.3 ADALIMUMAB 80 mg e.w.
ACR RESPONSE

An ACR 20 response was achieved by 54.16% of the adalimumab patients versus 10% of the placebo patients with an absolute risk difference of 44.16% (risk difference, 95%CI 0.44, 0.31-0.58). The relative risk (95%CI) was 5.42 (2.60-11.29) with a number needed to treat of 2.3.

An ACR 50 response was achieved by 19.44% of the adalimumab patients versus 1.42% of the placebo patients with an absolute risk difference of 18.02% (risk difference, 95%CI 0.8, 0.08-0.28). The relative risk (95%CI) was 13.61 (1.84-100.76) with a number needed to treat of 5.6.

An ACR 70 response was achieved by 8.33% of the adalimumab patients versus 0% of the placebo patients with an absolute risk difference of 8.33% (risk difference, 95%CI 0.08, 0.02-0.15). The relative risk (95%CI) was 12.64 (0.73-220.30) with a number needed to treat NNT of 12.0.

DAS 28

Mean change (SD) of the DAS 28 was -2.00 (1.20) in the adalimumab patients versus -0.50 (1.10) in the placebo patients with an absolute benefit of -1.50 and a relative difference of 21.12%. The weighted mean difference (95%CI) was -1.50 (-1.88 to -1.12).

EVIDENCE LEVEL: SILVER

B.2. EFFICACY AT 24/26 WEEKS

For the purpose of this review, weeks 24 and 26 were considered the same time point. Data of two studies (Van de Putte 2004; Furst 2003) were available.

B.2.1. ADALIMUMAB 20 mg e.w.

Data from one only study (Van de Putte 2004) were available

ACR AND EULAR RESPONSES

An ACR 20 response was achieved by 39.28% of the adalimumab patients versus 19.10% of the placebo patients with an absolute risk difference of 20.18% (risk difference, 95%CI 0.20, 0.09-0.32). The relative risk (95%CI) was 2.06 (1.31-3.22) with a number needed to treat NNT of 4.9.

An ACR 50 response was achieved by 20.53% of the adalimumab patients versus 8.18% of the placebo patients with an absolute risk difference of 12.35 (risk difference, 95%CI 0.12, 0.03-0.21). The relative risk (95%CI) was 2.51 (1.22-5.18) with a number needed to treat of 8.1.

An ACR 70 response was achieved by 9.82% of the adalimumab patients versus 1.81% of the placebo patients with an absolute risk difference of 8.01% (risk difference, 95%CI 0.08, 0.02-0.14). The relative risk (95%CI) was 5.40 (1.23-23.81) with a number needed to treat of 12.5.

An at least moderate EULAR response was achieved by 48.21% of the adalimumab patients versus 26.36% of the placebo patients with an absolute risk difference of 21.85% (risk difference, 95%CI 0.22, 0.09-0.34). The relative risk (95%CI) was 1.83 (1.27-2.64) with a number needed to treat of 4.6.

A good EULAR response was achieved by 9.82% of the adalimumab patients versus 3.63% of the placebo patients with an absolute risk difference of 6.19% (risk difference, 95%CI 0.06,

0.00-0.13). The relative risk (95%CI) was 2.70 (0.89-8.23).

DAS 28

Mean change (SD) of the DAS 28 was -1.60 (1.70) in the adalimumab patients versus -0.70 (1.30) in the placebo patients with an absolute benefit -0.90 and a RD of 12.67%. The weighted mean difference (95%CI) was -0.90 (-1.30 to -0.50).

EVIDENCE LEVEL: GOLD

B.2.2. ADALIMUMAB 20 mg e.o.w.

Data from one only study (Van de Putte 2004) were available.

ACR AND EULAR RESPONSES

An ACR 20 response was achieved by 35.84% of the adalimumab patients versus 19.10% of the placebo patients with an absolute risk difference of 16.74% (risk difference, 95%CI 0.17, 0.05-0.28). The relative risk (95%CI) was 1.88 (1.18-2.98) with a number needed to treat of 6.0.

An ACR 50 response was achieved by 18.86% of the adalimumab patients versus 8.18% of the placebo patients with an absolute risk difference of 10.68% (risk difference, 95%CI 0.11, 0.02-0.20). The relative risk (95%CI) was 2.31 (1.10-4.83) with a number needed to treat of 9.4.

An ACR 70 response was achieved by 8.49% of the adalimumab patients versus 1.81% of the placebo patients with an absolute risk difference of 6.68% (risk difference, 95%CI 0.07, 0.01-0.13). The relative risk (95%CI) was 4.67 (1.03-21.11) with a number needed to treat of 15.0.

An at least moderate EULAR response was achieved by 41.51% of the adalimumab patients versus 26.36% of the placebo patients with an absolute risk difference of 15.15% (risk difference, 95%CI 0.15, 0.03-0.28). The relative risk (95%CI) was 1.57 (1.07-2.32) with a number needed to treat of 6.6.

A good EULAR response was achieved by 6.60% of the adalimumab patients versus 3.63% of the placebo patients with an absolute risk difference of 2.97% (risk difference, 95%CI 0.03, -0.03-0.09). The relative risk (95%CI) was 1.82 (0.55-6.02).

DAS 28

Mean change (SD) of the DAS 28 was -1.30 (1.60) in the adalimumab patients versus -0.70 (1.30) in the placebo patients with an absolute benefit of -0.60 and a relative difference of 8.45%. The weighted mean difference (95%CI) was -0.60 (-0.99 to -0.21).

EVIDENCE LEVEL: GOLD

B.2.3. ADALIMUMAB 40 mg e.w.

Data from one only study (Van de Putte 2004) were available.

ACR AND EULAR RESPONSES

An ACR 20 response was achieved by 53.39% of the adalimumab patients versus 19.10% of the placebo patients with an absolute risk difference of 34.29% (risk difference, 95%CI 0.34, 0.22-0.46). The relative risk (95%CI) was 2.80 (1.83-4.28) with a number needed to treat of 2.9.

An ACR 50 response was achieved by 34.95% of the adalimumab patients versus 8.18% of the placebo patients with an absolute risk difference of 26.77% (risk difference, 95%CI 0.27, 0.16-0.37).

The relative risk (95%CI) was 4.27 (2.17-8.43) with a number needed to treat of 3.7.

An ACR 70 response was achieved by 18.44% of the adalimumab patients versus 1.81% of the placebo patients with an absolute risk difference of 16.63% (risk difference, 95%CI 0.17, 0.09-0.25). The relative risk (95%CI) was 10.15 (2.42-42.18) with a number needed to treat of 6.0.

An at least moderate EULAR response was achieved by 63.10% of the adalimumab patients versus 26.36% of the placebo patients with an absolute risk difference of 36.74% (risk difference, 95%CI 0.37, 0.24-0.49). The relative risk (95%CI) was 2.39 (1.69-3.38) with a number needed to treat of 2.7.

A good EULAR response was achieved by 13.59% of the adalimumab patients versus 3.63% of the placebo patients with an absolute risk difference of 9.96% (risk difference, 95%CI 0.10, 0.02-0.17). The relative risk (95%CI) was 3.74 (1.27-10.99) with a number needed to treat of 10.0.

DAS 28 AND COMPONENTS OF ACR RESPONSE DAS 28

Mean change (SD) of the DAS 28 was -2.00 (1.60) in the adalimumab patients versus -0.70 (1.30) in the placebo patients with an absolute benefit of -1.30 and a relative difference of 18.31%. The weighted mean difference (95%CI) was -1.30 (-1.69 to -0.91).

Tender Joints (TJ)

Mean change (SD) of the TJ was -17.10 (15.50) in the adalimumab patients versus -6.60 (16.60) in the placebo patients with an absolute benefit of -10.50 and a relative difference of 29.57%. The weighted mean difference (95%CI) was -10.50 (-14.81 to -6.19).

Swollen Joints (SJ)

Mean change (SD) of the SW was -8.30 (10.80) in the adalimumab patients versus -2.40 (9.50) in the placebo patients with an absolute benefit of -5.90 and a relative difference of 29.79%. The weighted mean difference (95%CI) was -5.90 (-8.64 to -3.16).

Patient Pain Assessment (PPA)

Mean change (SD) of the PPA was -32.00 (31.30) in the adalimumab patients versus -11.00 (26.70) in the placebo patients with an absolute benefit of -21.00 and a relative difference of 29.91%. The weighted mean difference (95%CI) was -21.00 (-28.84 to -13.16).

Patient Global Assessment (PGA)

Mean change (SD) of the PGA was -35.00 (31.50) in the adalimumab patients versus -10.60 (27.80) in the placebo patients with an absolute benefit of -24.40 and a relative difference of 33.98%. The weighted mean difference (95%CI) was -24.40 (-32.40 to -16.40).

Physician Global Assessment (PhyGA)

Mean change (SD) of the PhyGA was -32.50 (27.30) in the adalimumab patients versus -10.90 (25.40) in the placebo patients with an absolute benefit of -21.60 and a relative difference of 31.53%. The weighted mean difference (95%CI) was -21.60 (-28.69 to -14.51).

Health Assessment Questionnaire (HAQ)

Mean change (SD) of the HAQ was -0.49 (0.54) in the adalimumab patients versus -0.07 (0.49) in the placebo patients with an absolute benefit of -0.42 and a relative difference of 22.34%. The weighted mean difference (95%CI) was -0.42 (-0.56 to -0.28).

EVIDENCE LEVEL: GOLD

B.2.4. ADALIMUMAB 40 mg e.o.w.

Data from two studies (Van de Putte 2004; Furst 2003) were available

ACR AND EULAR RESPONSES

In Furst 2003, an ACR 20 response was achieved by 49.12% of the adalimumab patients versus 33.33% of the placebo patients with an absolute risk difference of 15.79% (risk difference, 95%CI 0.16, -0.03-0.34). The relative risk (95%CI) was 1.47 (0.91-2.38). In Van de Putte 2004, an ACR 20 response was achieved by 46.01% of the adalimumab patients versus 19.10% of the placebo patients with an absolute risk difference of 26.91% (risk difference, 95%CI 0.27, 0.15-0.39). The relative risk (95%CI) was 2.41 (1.56-3.72) with a number needed to treat of 3.7. As significant heterogeneity was not found, data from the two studies including 328 patients were pooled. An ACR 20 response was achieved by 47.05% of the adalimumab patients versus 23.41% of the placebo patients with a weighted risk difference (95%CI) of 0.24 (0.14-0.34). The relative risk (95%CI) was 1.91 (1.17-3.10) with a number needed to treat (95%CI) of 5.0 (3.0-9.0).

In Furst 2003, an ACR 50 response was achieved by 26.31% of the adalimumab patients versus 8.33% of the placebo patients with an absolute risk difference of 17.98% (risk difference, 95%CI 0.18, 0.04-0.32). The relative risk (95%CI) was 3.16 (1.12-8.88) with a number needed to treat of 5.6. In Van de Putte 2004, an ACR 50 response was achieved by 22.12% of the adalimumab patients versus 8.18% of the placebo patients with an absolute risk difference of 13.94% (risk difference, 95%CI 0.14, 0.05-0.23). The relative risk (95%CI) was 2.70 (1.32-5.53) with a number needed to treat of 7.2. As significant heterogeneity was not found, data from the two studies including 328 patients were pooled. An ACR 50 response was achieved by 23.53% of the adalimumab patients versus 8.22% of the placebo patients with a weighted risk difference (95%CI) of 0.15 (0.08-0.23). The relative risk (95%CI) was 2.84 (1.58-5.12) with a number needed to treat (95%CI) of 7.0 (4.0-20.0).

In Furst 2003, an ACR 70 response was achieved by 17.54% of the adalimumab patients versus 2.08% of the placebo patients with an absolute risk difference of 15.46% (risk difference, 95%CI 0.15, 0.05-0.26). The relative risk (95%CI) was 8.42 (1.12-63.45) with a number needed to treat of 6.5. In Van de Putte 2004, an ACR 70 response was achieved by 12.39% of the adalimumab patients versus 1.81% of the placebo patients with an absolute risk difference of 10.58% (risk difference, 95%CI 0.11, 0.04-0.17). The relative risk (95%CI) was 6.81 (1.59-29.29) with a number

needed to treat of 9.4. As significant heterogeneity was not found, data from the two studies including 328 patients were pooled. An ACR 70 response was achieved by 14.11% of the adalimumab patients versus 1.89% of the placebo patients with a weighted risk difference (95%CI) of 0.12 (0.06-0.18). The relative risk (95%CI) was 7.33 (2.25-23.90) with a number needed to treat (95%CI) of 9.0 (3.0-38.0).

In Van de Putte 2004, an at least moderate EULAR response was achieved by 55.75% of the adalimumab patients versus 26.36% of the placebo patients with a absolute risk difference of 29.39% (risk difference, 95%CI 0.29, 0.17-0.42). The relative risk (95%CI) was 2.11 (1.49-3.01) with a number needed to treat of 3.4.

In Van de Putte 2004, a good EULAR response was achieved by 8.85% of the adalimumab patients versus 3.63% of the placebo patients with a absolute risk difference of 5.22% (risk difference, 95%CI 0.05, -0.01-0.12). The relative risk (95%CI) was 2.43 (0.79-7.53).

DAS 28 AND COMPONENTS OF ACR RESPONSE DAS 28

In Van de Putte 2004, mean change (SD) of the DAS 28 was - 1.70 (1.60) in the adalimumab patients versus -0.70 (1.30) in the placebo patients with an absolute benefit of -1.00 and a relative difference of 14.08%. The weighted mean difference (95%CI) was -1.00 (-1.38 to -0.62).

Tender Joint (TJ)

In Van de Putte 2004, mean change (SD) of the TJ was -13.60 (18.70) in the adalimumab patients versus -6.60 (16.60) in the placebo patients with an absolute benefit of -7.00 and a relative difference of 19.71%. The weighted mean difference (95%CI) was -7.00 (-11.64 to -2.36).

Swollen Joints (SJ)

In Van de Putte 2004, mean change (SD) of the SJ was -8.50 (10.60) in the adalimumab patients versus -2.40 (9.50) in the placebo patients with an absolute benefit of -6.10 and a relative difference of 30.80%. The weighted mean difference (95%CI) was -6.10 (-8.74 to -3.46).

Patient Pain Assessment (PPA)

In Van de Putte 2004, mean change (SD) of the PPA was -27.60 (31.10) in the adalimumab patients versus -11.00 (26.70) in the placebo patients with an absolute benefit of -16.60 and a relative difference of 23.64%. The weighted mean difference (95%CI) was -16.60 (-24.20 to -9.00).

Patient Global Assessment (PGA)

In Van de Putte 2004, mean change (SD) of the PGA was -27.90 (30.50) in the adalimumab patients versus -10.60 (27.80) in the placebo patients with an absolute benefit of -17.30 and a relative difference of 24.09%. The weighted mean difference (95%CI) was -17.30 (-24.96 to -9.64).

Physician Global Assessment (PhyGA)

In Van de Putte 2004, mean change (SD) of the PhyGA was -27.30 (28.80) in the adalimumab patients versus -10.90 (25.40) in the placebo patients with an absolute benefit of -16.40 and

a relative difference of 23.94%. The weighted mean difference (95%CI) was -16.40 (-23.52 to -9.28).

Health Assessment Questionnaire (HAQ)

In Van de Putte 2004, mean change (SD) of the HAQ was -0.38 (0.60) in the adalimumab patients versus -0.07 (0.49) in the placebo patients with an absolute benefit of -0.31 and a relative difference of 16.49%. The weighted mean difference (95%CI) was -0.31 (-0.45 to -0.17).

EVIDENCE LEVEL: GOLD

B.3. SAFETY

Data were analysed considering all doses of adalimumab and all periods of treatment. Data from three studies (Furst 2003, Van de Putte 2003, and Van de Putte 2004) were available.

AEs

Data about adverse events were available in Furst 2003, and Van de Putte 2004, including 676 patients. In Furst 2003, 80.7% of the adalimumab patients had any AEs versus 48% of the placebo patients with an absolute risk difference of 32.7% (risk difference, 95%CI 0.33, 0.17-0.48). The relative risk (95%CI) was 1.68(1.29-2.20) with a number needed to harm of 3.0. In Van de Putte 2004, 98.84% of the adalimumab patients had any AEs versus 95.45 of the placebo patients (not significant difference). Significant heterogeneity was found, thus data were not pooled. The most frequent AEs were upper respiratory tract infections, rhinitis, and headache.

SAEs

In Furst 2003, 5.26% of the adalimumab patients had any SAEs versus 4.16% of the placebo patients (not significant difference). In Van de Putte 2003, 7.47% of the adalimumab patients had any SAEs versus a 10% of the placebo patients (not significant difference). In Van de Putte 2004, 12.21% of the adalimumab patients had any SAEs versus 14.54% of the placebo patients (not significant difference). As significant heterogeneity was not found, data from the three studies including 933 patients were pooled. 10.21% of the adalimumab patients had any adverse event versus 10.96% of the placebo patients (not significant difference).

Withdrawals due to AEs

In Furst 2003, 3.5% of the adalimumab patients withdrew due to AEs versus 2.08% of the placebo patients (not significant difference). In Van de Putte 2003, 2.33% of the adalimumab patients withdrew due to AEs versus 1.42% of the placebo patients (not significant difference). In Van de Putte 2004, 3.68% of the adalimumab patients withdrew due to AEs versus 0.90% of the placebo patients (not significant difference). As significant heterogeneity was not found, data from the three studies including 933 patients were pooled. A 3.26% of the adalimumab patients withdrew due to AEs versus 1.31% of the placebo patients but the difference was not statistically significant in terms of relative nor absolute risk.

Infections

Data about the frequency of infections were only available in Furst 2003. Infections happened in 49.12% of the adalimumab patients

versus 35.41% of the placebo patients. The difference was not statistically significant in terms of relative nor absolute risk.

Serious infections

In Furst 2003, none patient with adalimumab in monotherapy or placebo had a serious infection. In Van de Putte 2003, serious infections happened in 1.87% of the adalimumab patients versus 0% of the placebo patients (not statistically significant difference). In Van de Putte 2004, 2.3% of the adalimumab patients had serious infections versus 0% of the placebo patients (not statistically significant difference). As significant heterogeneity was not found, data from the three studies including 933 patients were pooled. 1.98% of the adalimumab patients had serious infections versus 0% of the placebo patients. The difference was not statistically significant in terms of relative nor absolute risk.

Positive ANA and anti-DNA antibodies

In Van de Putte 2003, a 46.94% of the adalimumab patients had positive ANA versus 37.14% of the placebo patients (not significant difference). In Van de Putte 2004, 12.21% of the adalimumab patients had positive ANA versus 5.45% of the placebo patients with a absolute risk difference of 6.76 (risk difference, 95% CI 0.07, 0.02-0.12). The relative risk (95%CI) was 2.24 (0.99-5.07) with a number needed to harm of 14.8. As significant heterogeneity was not found, data from the two studies including 827 patients were pooled. 23.64% of the adalimumab patients has positive ANA versus a 17.77% of the placebo patients with a weighted risk difference (95%CI) of 0.07 (0.02-0.12). The relative risk (95%CI) was 1.50 (0.88-2.55) with a number needed to harm (95%CI) of 11.0 (6.0-87.0).

Data about anti-DNA were only available in Van de Putte 2003. 3% of the adalimumab patients had positive anti-DNA versus 0% of the placebo patients (not significant difference).

Withdrawals

Data were available in Van de Putte 2003, and Van de Putte 2004. Withdrawals were significantly less frequent in adalimumab patients than in placebo patients (relative risk, 95%CI 0.47, 0.38-0.57).

DISCUSSION

We have performed a systematic review about the efficacy and safety of adalimumab, a fully human anti-TNF alpha monoclonal antibody, for treating rheumatoid arthritis. The approved dose of adalimumab is 40 mg subcutaneously (sc) every other week (e.o.w.) in combination with methotrexate or in monotherapy. When administered as monotherapy, the dose can be increased to 40 mg every week (e.w.) if the response to the approved dose is not adequate. However, the published studies include several subcutaneous doses e.w. or e.o.w. All of them have been considered in this review in which two comparisons were analysed: Adalimumab sc+methotrexate (or DMARDs) versus placebo sc+ methotrexate (or DMARDs), and adalimumab sc in monotherapy versus placebo

sc. Studies with adalimumab intravenous were excluded because it is not available to be used in clinical practice.

This meta-analysis supports the efficacy at 24 and 52 weeks of adalimumab sc in combination with methotrexate measured by the ACR response core set. At 24 weeks, the NNTs to achieve an ACR 20/50/70 with adalimumab 40 mg sc e.o.w. range from 1.89 to 7. Other doses of adalimumab are also efficacious but the NNTs are slightly higher with adalimumab 20 mg e.o.w. The doses of 20 mg e.w. and 80 mg e.o.w have similar efficacy than the approved dose. At 52 weeks, only two doses, 20 mg e.w. and 40 mg e.o.w. have been analysed. With adalimumab 40 mg e.o.w. the NNTs to achieve an ACR 20/50/70 range from 2.86 to 5.35. With adalimumab 20 mg e.w. the efficacy is similar. Both doses significantly slow the radiographic progression at 52 weeks but the effect size is higher with 40 mg e.o.w. than with 20 mg e.w.

This review also supports the efficacy of adalimumab in monotherapy at 12 and 24 weeks. At 12 weeks, only weekly doses (20, 40, and 80 mg) have been studied and the efficacy is similar between them. At 24/26 weeks the efficacy with the dose of 40 mg (e.w. or e.o.w.) is higher than with 20 mg (e.w. or e.o.w.). With adalimumab 40 mg e.o.w. the NNTs to achieve an ACR 20/50/70 range from 5 to 9, whereas with adalimumab 40 mg e.w. these NNTs are slightly lower and range from 2.91 to 6.01.

The other approved anti-TNF agents, infliximab and etanercept, have also demonstrated clinical efficacy and favourable effect on radiographic progression in RA patients. There were no comparative studies between anti-TNF agents, even though efficacy patterns seem be similar. However, there are studies that show efficacy of infliximab and etanercept in early RA, whereas studies with adalimumab are on RA patients with longstanding disease and failure to previous DMARDs.

The safety profile of adalimumab is favourable, without significant differences versus control groups in most of the considered items but positive ANA are consistently more common in adalimumab groups, even though they are not clinically relevant. Serious infections were significantly more frequent with adalimumab in combination with methotrexate in the longer study (Keystone 2004) with a NNH of 30.21.

The level of evidence of the conclusions ranges from silver to gold and there are not any conclusions with a platinum level of evidence. This is due to two main reasons: first, the number of studies on adalimumab is limited and many different doses were administered. So, in many cases, i. e. radiographic outcomes, data from only one study were available and pooling was not possible. Second, although all studies have an acceptable methodological quality, some of them did not meet all needed criteria for reaching a gold evidence level. It was mainly due to the fact that allocation concealment was not clearly described in some of the studies.

A random effects model was chosen for the analysis due to the fact it yields a more conservative estimation of the results. In the most of the analyzed comparisons there was no heterogeneity and the results did not change when analyzed using fixed or random effects model (data not shown). Significant heterogeneity was found in some cases, mainly in the ACR 20 response at 24 weeks with adalimumab 40 mg sc e.o.w. in combination with methotrexate. The automatically pooled results were not considered due to the significant heterogeneity. The sources of heterogeneity are not clear. The ACR response rate on adalimumab group was higher in Weinblatt 2003 than in Furst 2003, and conversely, the ACR response rate on placebo group was higher in Furst 2003 than in Weinblatt 2003. However, when any of the two studies was excluded of the analysis, heterogeneity was also found. The characteristics of the included populations in all the considered studies (Furst 2003, Keystone 2004, and Weinblatt 2003) were similar, so the meaning of this heterogeneity remains uncertain.

All of the studies included rheumatoid arthritis patients with a long standing disease who had failed to DMARDs. However, there are no published clinical trials in early rheumatoid arthritis nor in DMARDs naive patients.

AUTHORS' CONCLUSIONS

Implications for practice

On the basis of the studies reviewed here, it can be said that:

Adalimumab in combination with methotrexate is efficacious and safe in the treatment of the rheumatoid arthritis.

Adalimumab 20 mg e.w. and 40 mg sc e.o.w. slows the radiographic progression at 52 weeks.

Adalimumab in combination with DMARDs other than methotrexate is also efficacious and safe, even though data are from only one study and the number of patients in each group is low.

Adalimumab in monotherapy is efficacious and safe in the treatment of the rheumatoid arthritis even though the effect size is lower than with combined therapy.

Implications for research

The available clinical trials with adalimumab are short-term studies (six-months duration) and there is only one twelve-month study. Long-term efficacy and safety studies are needed. There are some published open extension trials with available data about effectiveness, effect on the radiographic progression, and safety. Other uncontrolled long-terms studies are ongoing.

The efficacy and the effect on the radiographic progression of adalimumab in patients with early rheumatoid arthritis and in DMARDs naive patients must be assessed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Furst 2003

Methods	Randomized, double-blind, 24-weeks, placebo-controlled study	
Participants	636 RA patients with active disease (at least 9 tender and 6 swollen joints)	
Interventions	Adalimumab s.c. 40 mg e.o.w or placebo. DMARDs allowed.	
Outcomes	ACR response.	
Notes	The main outcome was safety	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Keystone 2004

Methods	Randomized, double-blind, 52-weeks, placebo-controlled study
Participants	619 RA patients with active disease (at least 9 tender and 6 swollen joints and CPR>1 mg/dl. Positive RF and at least 1 erosion required
Interventions	Adalimumab s.c. 40 mg e.o.w., 20 mg e.w., or placebo. Concomitant treatment with methotrexate
Outcomes	ACR response, tender and swollen joints, patient pain assessment, patient and physician global assessments, CPR, HAQ, radiographics indexes
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rau 2004

Methods	Randomized, double-blind, placebo-controlled study.
Participants	54 RA patients with active disease (DAS>3.2).
Interventions	Adalimumab i.v. or s.c. 1 mg/kg or placebo once. Concomitant treatment with methotrexate. A second injection at 1-3 months according response
Outcomes	EULAR and ACR responses, DAS, tender and swollen joints, patient pain assessment, patient and physician global assessment, HAQ, CRP, ESR
Notes	It was followed by an open-label extension.
Risk of bias	

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Van de Putte 2003

Methods	Randomized, double-blind, 12-week, placebo-controlled study.
Participants	284 RA patients with active disease (at least 12 tender and 10 swollen joints, ESR>28, CRP>20mg/l
Interventions	Adalimumab s.c. 20, 40 or 80 mg e.w. or placebo. DMARDs not allowed
Outcomes	ACR response, tender and swollen joints, patient pain assessment, patient and physician global assessments, HAQ, DAS28, CRP, ESR
Notes	Double-blind phase followed by an open-label continuation.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Van de Putte 2004

Methods	Randomized, double-blind, 26-weeks, placebo-controlled study
Participants	544 RA patients with active disease (12 tender and 10 swollen joints, ESR>28, CRP>20 mg/l
Interventions	Adalimumab s.c. 20 mg e.w. or e.o.w., 40 mg e.w. or e.o.w. or placebo. DMARDs not allowed
Outcomes	ACR and EULAR response, tender and swollen joints, patient pain assessment, patient and physician global assessments, DAS28, HAQ, ESR, CRP

Van de Putte 2004 (Continued)

Notes	It was followed by an open-label extension.	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Weinblatt 2003

Methods	Randomized, double-blind, 24-weeks, placebo-controlled study
Participants	271 RA patients with active disease (at least 9 tender and 6 swolen joints
Interventions	Adalimumab s.c. 20, 40 or 80 mg every other week or placebo. Concomitant treatment with methotrexate
Outcomes	ACR response, tender and swollen joints, patient pain assessment, patient and physician global assessments, HAQ, CRP, SF-36
Notes	

Risk of bias

It	tem	Authors' judgement	Description
A	llocation concealment?	Yes	A - Adequate

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Barrera 2002	Study that compared the results of several studies with adalimumab (different doses) versus those of one study with methotrexate. Patients with adalimumab received the anti-TNF in a double-blind manner (vs placebo) during the first 6 weeks but the results comparing with placebo were not reported
Den Broeder 2002a	Randomized, double-blind, multicentre, placebo-controlled study comparing a single dose of adalimumab iv 0.5, 1, 3, 5, or 10 mg/kg vs placebo
Den Broeder 2002b	Open study of dose reduction in RA patients treated with adalimumab participating in an open extension study
Den Broeder 2002c	Open study on RA patients initially included in a randomized, placebo-controlled trial of adalimumab in monotherapy. Radiological assessments were done at baseline, one and two years. Since week 6-8 all of patients received adalimumab in an open manner

(Continued)

Den Broeder 2003	Study of the effects of adalimumab on the neutrophil migration. Patients were participating in randomized, double-blind studies of adalimumab (20 to 80 mg s.c.). EULAR response at week 2 was reported, but the doses of adalimumab were not specified
Keystone 2003	Subanalysis of the clinical and radiographic response to adalimumab in the DE019 study (included in this revision and named as Keystone 2004)
Schatenkirchner 1998	Randomised, double-blind, 3-month, placebo-controlled study in 24 RA patients followed by an open-label, 3 month phase. Data comparing to placebo were not reported
Tjioe 2003	Open study to assess the influence of adalimumab on ultraviolet response of the skin of RA patients
Velagapudi 2004	Randomized, double-blind, placebo controlled study of Adalimumab 40 mg s.c. every other week vs placebo in RA patients continuing with methotrexate. It is published as EULAR 2004 abstract and complete data are not provided
Weisman 2003	Randomized, double-blind, multicentre, placebo-controlled study comparing adalimumab iv 0.25, 0.5, 1, 3, or 5 mg/kg vs placebo

DATA AND ANALYSES

Comparison 1. Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 week 16, 20 mg e.o. week	1	131	Risk Ratio (M-H, Random, 95% CI)	2.49 [1.46, 4.24]
1.2 Week 16, 40 mg e.o. week	1	129	Risk Ratio (M-H, Random, 95% CI)	3.35 [2.01, 5.56]
1.3 Week 16, 80 mg e.o. week	1	135	Risk Ratio (M-H, Random, 95% CI)	2.94 [1.75, 4.93]
1.4 week 24, 20 mg e. week	1	412	Risk Ratio (M-H, Random, 95% CI)	2.06 [1.62, 2.62]
1.5 week 24 20 mg e.o.week	1	131	Risk Ratio (M-H, Random, 95% CI)	3.29 [1.72, 6.33]
1.6 Week 24, 40 mg e.o week	3	1067	Risk Ratio (M-H, Random, 95% CI)	2.24 [1.43, 3.52]
1.7 Week 24, 80 mg e.o. week	1	135	Risk Ratio (M-H, Random, 95% CI)	4.53 [2.42, 8.47]
1.8 Week 52, 20 mg e. week	1	412	Risk Ratio (M-H, Random, 95% CI)	2.28 [1.73, 3.00]
1.9 Week 52, 40 mg e.o.week	1	407	Risk Ratio (M-H, Random, 95% CI)	2.46 [1.87, 3.22]
1.10 Week 4 (period), 1	1	36	Risk Ratio (M-H, Random, 95% CI)	2.4 [1.06, 5.41]
mg/kg, once				
2 ACR50	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 week 24, 20 mg e. week	1	412	Risk Ratio (M-H, Random, 95% CI)	4.32 [2.73, 6.82]
2.2 week 24 20 mg e.o.week	1	131	Risk Ratio (M-H, Random, 95% CI)	3.95 [1.59, 9.81]
2.3 Week 24, 40 mg e.o week	3	1067	Risk Ratio (M-H, Random, 95% CI)	3.73 [2.21, 6.29]
2.4 Week 24, 80 mg e.o. week	1	135	Risk Ratio (M-H, Random, 95% CI)	5.27 [2.18, 12.72]
2.5 Week 52, 20 mg e. week	1	412	Risk Ratio (M-H, Random, 95% CI)	3.97 [2.50, 6.30]
2.6 Week 52, 40 mg e.o.week	1	407	Risk Ratio (M-H, Random, 95% CI)	4.37 [2.77, 6.91]
2.7 Week 4 (period) 1 mg/kg,	1	36	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.39, 126.48]
once				
3 ACR70	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 week 24, 20 mg e. week	1	412	Risk Ratio (M-H, Random, 95% CI)	6.98 [2.80, 17.41]
3.2 week 24 20 mg e.o.week	1	131	Risk Ratio (M-H, Random, 95% CI)	2.10 [0.57, 7.76]
3.3 Week 24, 40 mg e.o week	3	1067	Risk Ratio (M-H, Random, 95% CI)	5.14 [3.14, 8.41]
3.4 Week 24, 80 mg e.o. week	1	135	Risk Ratio (M-H, Random, 95% CI)	3.96 [1.19, 13.16]
3.5 Week 52, 20 mg e. week	1	412	Risk Ratio (M-H, Random, 95% CI)	4.61 [2.31, 9.20]
3.6 Week 52, 40 mg e.o.week	1	407	Risk Ratio (M-H, Random, 95% CI)	5.15 [2.60, 10.22]
4 EULAR response good	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Week 4 (period), 1 mg/kg	1	36	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.39, 126.48]
once				
5 EULAR response moderate	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Week 4 (period), 1 mg/kg once	1	36	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.73, 2.59]
6 Withdrawals	2	1163	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.74, 1.19]
7 Adverse events (all doses of adalimumab)	3	1186	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.99, 1.08]
8 Serious adverse events (all doses of Adalimumab)	2	567	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.39, 1.40]
9 Withdrawals due to adverse events (all doses of adalimumab)	4	1457	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.83, 2.25]

10 Infections (all doses of adalimumab)	1	531	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.87, 1.20]
11 Serious infections (all doses of Adalimumab)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12 Tender joints	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 Week 24, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-7.30 [-9.87, -4.73]
12.2 Week 24, 20 mge.o. week	1	131	Mean Difference (IV, Random, 95% CI)	-9.10 [-13.77, -4.43]
12.3 Week 24, 40 mg e.o. week	2	536	Mean Difference (IV, Random, 95% CI)	-6.68 [-9.02, -4.34]
12.4 week 24, 80 mg e.o week	1	135	Mean Difference (IV, Random, 95% CI)	-11.50 [-15.87, -7. 13]
12.5 Week 52, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-7.20 [-9.96, -4.44]
12.6 Week 52, 40 mg e.o. week	1	407	Mean Difference (IV, Random, 95% CI)	-7.00 [-9.68, -4.32]
13 Swollen joints	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
13.1 Week 24, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-5.80 [-7.77, -3.83]
13.2 Week 24, 20 mge.o. week	1	131	Mean Difference (IV, Random, 95% CI)	-4.80 [-8.32, -1.28]
13.3 Week 24, 40 mg e.o. week	2	536	Mean Difference (IV, Random, 95% CI)	-5.86 [-7.90, -3.82]
13.4 week 24, 80 mg e.o week	1	65	Mean Difference (IV, Random, 95% CI)	-7.9 [-17.76, 1.96]
13.5 Week 52, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-6.1 [-8.15, -4.05]
13.6 Week 52, 40 mg e.o. week	1	407	Mean Difference (IV, Random, 95% CI)	-6.30 [-8.37, -4.23]
14 Patient pain assessment	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 Week 24, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-15.30 [-20.43, -10. 17]
14.2 Week 24, 20 mge.o. week	1	131	Mean Difference (IV, Random, 95% CI)	-16.20 [-24.20, -8. 20]
14.3 Week 24, 40 mg e.o. week	2	536	Mean Difference (IV, Random, 95% CI)	-15.79 [-20.27, -11. 32]
14.4 week 24, 80 mg e.o week	1	135	Mean Difference (IV, Random, 95% CI)	-19.0 [-26.97, -11. 03]
14.5 Week 52, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-16.2 [-21.63, -10. 77]
14.6 Week 52, 40 mg e.o. week	1	407	Mean Difference (IV, Random, 95% CI)	-18.2 [-23.46, -12. 94]
15 Patient global assessment	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
15.1 Week 24, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-13.30 [-18.65, -7. 95]
15.2 Week 24, 20 mge.o. week	1	131	Mean Difference (IV, Random, 95% CI)	-18.5 [-27.03, -9.97]
15.3 Week 24, 40 mg e.o. week	2	536	Mean Difference (IV, Random, 95% CI)	-17.01 [-21.71, -12. 31]
15.4 week 24, 80 mg e.o week	1	135	Mean Difference (IV, Random, 95% CI)	-23.4 [-32.02, -14. 78]
15.5 Week 52, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-13.20 [-18.89, -7. 51]
15.6 Week 52, 40 mg e.o. week	1	407	Mean Difference (IV, Random, 95% CI)	-16.6 [-22.32, -10. 88]

16 Physician global assessment	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1 Week 24, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-15.20 [-19.98, -10. 42]
16.2 Week 24, 20 mge.o. week	1	131	Mean Difference (IV, Random, 95% CI)	-23.5 [-31.60, -15. 40]
16.3 Week 24, 40 mg e.o. week	2	536	Mean Difference (IV, Random, 95% CI)	-19.42 [-27.19, -11.
16.4 week 24, 80 mg e.o week	1	135	Mean Difference (IV, Random, 95% CI)	-31.2 [-39.20, -23. 20]
16.5 Week 52, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-16.70 [-21.56, -11. 84]
16.6 Week 52, 40 mg e.o. week	1	407	Mean Difference (IV, Random, 95% CI)	-19.9 [-24.58, -15. 22]
17 HAQ	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
17.1 Week 24, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.46, -0.26]
17.2 Week 24, 20 mge.o. week	1	131	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.47, -0.07]
17.3 Week 24, 40 mg e.o. week	2	536	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.42, -0.23]
17.4 week 24, 80 mg e.o week	1	135	Mean Difference (IV, Random, 95% CI)	-0.32 [-0.51, -0.13]
17.5 Week 52, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.47, -0.25]
17.6 Week 52, 40 mg e.o.	1	407	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.45, -0.23]
week			()	
18 CRP	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
18.1 Week 24, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-0.60 [-0.87, -0.33]
18.2 Week 24, 20 mge.o.	1	131	Mean Difference (IV, Random, 95% CI)	-1.5 [-2.41, -0.59]
week				
18.3 Week 24, 40 mg e.o. week	2	536	Mean Difference (IV, Random, 95% CI)	-1.21 [-2.09, -0.33]
18.4 week 24, 80 mg e.o week	1	135	Mean Difference (IV, Random, 95% CI)	-1.40 [-2.40, -0.40]
18.5 Week 52, 20 mg e. week	1	412	Mean Difference (IV, Random, 95% CI)	-0.6 [-0.92, -0.28]
18.6 Week 52, 40 mg e.o. week	1	407	Mean Difference (IV, Random, 95% CI)	-0.6 [-0.93, -0.27]
19 Modified Sharp Index	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
19.1 Week 52, 20 mg e. week	1	368	Mean Difference (IV, Random, 95% CI)	-1.90 [-3.13, -0.67]
19.2 Week 52, 40 mg e.o.	1	355	Mean Difference (IV, Random, 95% CI)	-2.6 [-3.83, -1.37]
week				
20 Erosion score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
20.1 Week 52, 20 mg e. week	1	368	Mean Difference (IV, Random, 95% CI)	-1.20 [-1.94, -0.46]
20.2 Week 52, 40 mg e.o.	1	355	Mean Difference (IV, Random, 95% CI)	-1.6 [-2.37, -0.83]
week			()	
21 Joint space index	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 Week 52, 40 mg e.o.	1	355	Mean Difference (IV, Random, 95% CI)	-0.9 [-1.46, -0.34]
week				
22 ANA (all doses of Adalimumab)	4	1335	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.20, 2.13]
23 AntiDNA (all doses of	3	1022	Risk Ratio (M-H, Random, 95% CI)	11.07 [4.05, 30.31]
adalimumab)				

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Week 2, 20 mg e.week	2	363	Risk Ratio (M-H, Random, 95% CI)	6.10 [3.24, 11.48]
1.2 Week 2, 20 mg e. o. week	1	216	Risk Ratio (M-H, Random, 95% CI)	5.19 [2.55, 10.56]
1.3 Week 2, 40 mg e. week	2	353	Risk Ratio (M-H, Random, 95% CI)	6.66 [2.33, 19.08]
1.4 Week 2, 40 mg e.o week	1	223	Risk Ratio (M-H, Random, 95% CI)	4.87 [2.39, 9.92]
1.5 Week 2, 80 mg e. week	1	142	Risk Ratio (M-H, Random, 95% CI)	16.04 [4.00, 64.33]
1.6 Week 12, 20 mg e. week	1	141	Risk Ratio (M-H, Random, 95% CI)	5.07 [2.42, 10.62]
1.7 Week 12 40 mg e. week	1	140	Risk Ratio (M-H, Random, 95% CI)	5.71 [2.75, 11.88]
1.8 Week 12, 80 mg e. week	1	142	Risk Ratio (M-H, Random, 95% CI)	5.42 [2.60, 11.29]
1.9 Week 24/26, 20 mg e. week	1	222	Risk Ratio (M-H, Random, 95% CI)	2.06 [1.31, 3.22]
1.10 Week 24/26, 20 mg e.o. week	1	216	Risk Ratio (M-H, Random, 95% CI)	1.88 [1.18, 2.98]
1.11 Week 24/26, 40 mg e. week	1	213	Risk Ratio (M-H, Random, 95% CI)	2.80 [1.83, 4.28]
1.12 Week 24/26, 40 mg e.o. week	2	328	Risk Ratio (M-H, Random, 95% CI)	1.91 [1.17, 3.10]
2 ACR 50	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Week 2, 20 mg e.week	2	363	Risk Ratio (M-H, Random, 95% CI)	8.79 [1.11, 69.87]
2.2 Week 2, 20 mg e. o. week	1	216	Risk Ratio (M-H, Random, 95% CI)	11.41 [0.64, 203.86]
2.3 Week 2, 40 mg e. week	2	353	Risk Ratio (M-H, Random, 95% CI)	15.09 [2.00, 113.99]
2.4 Week 2, 40 mg e.o week	1	223	Risk Ratio (M-H, Random, 95% CI)	22.39 [1.34, 375.46]
2.5 Week 2, 80 mg e. week	1	142	Risk Ratio (M-H, Random, 95% CI)	10.70 [0.60, 189.94]
2.6 Week 12, 20 mg e. week	1	141	Risk Ratio (M-H, Random, 95% CI)	16.76 [2.29, 122.56]
2.7 Week 12 40 mg e. week	1	140	Risk Ratio (M-H, Random, 95% CI)	19.00 [2.61, 138.08]
2.8 Week 12, 80 mg e. week	1	142	Risk Ratio (M-H, Random, 95% CI)	13.61 [1.84, 100.76]
2.9 Week 24/26, 20 mg e. week	1	222	Risk Ratio (M-H, Random, 95% CI)	2.51 [1.22, 5.18]
2.10 Week 24/26, 20 mg e.o. week	1	216	Risk Ratio (M-H, Random, 95% CI)	2.31 [1.10, 4.83]
2.11 Week 24/26, 40 mg e. week	1	213	Risk Ratio (M-H, Random, 95% CI)	4.27 [2.17, 8.43]
2.12 Week 24/26, 40 mg e.o. week	2	328	Risk Ratio (M-H, Random, 95% CI)	2.84 [1.58, 5.12]
3 ACR70	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Week 2, 20 mg e.week	2	363	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.2 Week 2, 20 mg e. o. week	1	216	Risk Ratio (M-H, Random, 95% CI)	3.11 [0.13, 75.56]
3.3 Week 2, 40 mg e. week	2	353	Risk Ratio (M-H, Random, 95% CI)	4.06 [0.45, 36.38]
3.4 Week 2, 40 mg e.o week	1	223	Risk Ratio (M-H, Random, 95% CI)	8.76 [0.48, 160.87]
3.5 Week 2, 80 mg e. week	1	142	Risk Ratio (M-H, Random, 95% CI)	2.92 [0.12, 70.44]
3.6 Week 12, 20 mg e. week	1	141	Risk Ratio (M-H, Random, 95% CI)	16.76 [0.99, 285.00]
3.7 Week 12 40 mg e. week	1	140	Risk Ratio (M-H, Random, 95% CI)	15.0 [0.87, 257.70]
3.8 Week 12, 80 mg e. week	1	142	Risk Ratio (M-H, Random, 95% CI)	12.64 [0.73, 220.30]
3.9 Week 24/26, 20 mg e.	1	222	Risk Ratio (M-H, Random, 95% CI)	5.40 [1.23, 23.81]
week	1	222	2001 2000 (271 22, 100100111, 7770 OI)	y. 10 [1.2J, 2J.01]

3.10 Week 24/26, 20 mg e.o. week	1	216	Risk Ratio (M-H, Random, 95% CI)	4.67 [1.03, 21.11]
3.11 Week 24/26, 40 mg e. week	1	213	Risk Ratio (M-H, Random, 95% CI)	10.15 [2.42, 42.48]
3.12 Week 24/26, 40 mg e.o. week	2	328	Risk Ratio (M-H, Random, 95% CI)	7.33 [2.25, 23.90]
4 EULAR response: at least	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
moderate	1	222	D. I D. : (MII D. I. OCO/ CI)	2 21 [2 02 5 (2]
4.1 Week 2, 20 mg e.week	1	222	Risk Ratio (M-H, Random, 95% CI)	3.31 [2.03, 5.42]
4.2 Week 2, 20 mg e. o. week	1	216	Risk Ratio (M-H, Random, 95% CI)	3.31 [2.02, 5.42]
4.3 Week 2, 40 mg e. week	1	213	Risk Ratio (M-H, Random, 95% CI)	3.34 [2.04, 5.47]
4.4 Week 2, 40 mg e.o week	1	223	Risk Ratio (M-H, Random, 95% CI)	3.47 [2.13, 5.65]
4.5 Week 24/26, 20 mg e. week	1	222	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.27, 2.64]
4.6 Week 24/26, 20 mg e.o. week	1	216	Risk Ratio (M-H, Random, 95% CI)	1.57 [1.07, 2.32]
4.7 Week 24/26, 40 mg e. week	1	213	Risk Ratio (M-H, Random, 95% CI)	2.39 [1.69, 3.38]
4.8 Week 24/26, 40 mg e.o. week	1	223	Risk Ratio (M-H, Random, 95% CI)	2.11 [1.49, 3.01]
5 EULAR response: good	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Week 2, 20 mg e.week	1	222	Risk Ratio (M-H, Random, 95% CI)	2.95 [0.12, 71.57]
5.2 Week 2, 20 mg e. o. week	1	216	Risk Ratio (M-H, Random, 95% CI)	5.19 [0.25, 106.79]
5.3 Week 2, 40 mg e. week	1	213	Risk Ratio (M-H, Random, 95% CI)	3.20 [0.13, 77.72]
5.4 Week 2, 40 mg e.o week	1	223	Risk Ratio (M-H, Random, 95% CI)	8.76 [0.48, 160.87]
5.5 Week 24/26, 20 mg e.	1	222	Risk Ratio (M-H, Random, 95% CI)	2.70 [0.89, 8.23]
week	1	222	rask ratio (ivi 11, randoni, 7570 Ci)	2.70 [0.07, 0.23]
5.6 Week 24/26, 20 mg e.o. week	1	216	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.55, 6.02]
5.7 Week 24/26, 40 mg e. week	1	213	Risk Ratio (M-H, Random, 95% CI)	3.74 [1.27, 10.99]
5.8 Week 24/26, 40 mg e.o. week	1	223	Risk Ratio (M-H, Random, 95% CI)	2.43 [0.79, 7.53]
6 Adverse events (all doses of adalimumab)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7 Serious adverse events (all doses of adalimumab)	3	933	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.54, 1.28]
8 Withdrawals due to adverse events (all doses of adalimumab)	3	933	Risk Ratio (M-H, Random, 95% CI)	2.34 [0.67, 8.10]
9 Infections	1	105	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.87, 2.21]
10 Serious infections (all doses of	3	933	Risk Ratio (M-H, Random, 95% CI)	4.02 [0.53, 30.59]
adalimumab)			, , , , , , , , , , , , , , , , , , , ,	
11 ANA (all doses of adalimumab)	2	827	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.88, 2.55]
12 AntiDNA	1	126	Risk Ratio (M-H, Random, 95% CI)	1.87 [0.10, 35.14]
13 DAS28	2	1 / 1	Mean Difference (IV, Random, 95% CI)	Subtotals only
13.1 Week 2, 20 mg e.week	1	141	Mean Difference (IV, Random, 95% CI)	-1.1 [-1.38, -0.82]
13.2 Week 2, 40 mg e.week	1	140	Mean Difference (IV, Random, 95% CI)	-1.4 [-1.71, -1.09]
13.3 Week 2, 80 mg e. week	1	142	Mean Difference (IV, Random, 95% CI)	-1.5 [-1.78, -1.22]
13.4 Week 12, 20 mg e. w.	1	141 140	Mean Difference (IV, Random, 95% CI)	-1.3 [-1.72, -0.88]
13.5 Week 12, 40 mg, e.w.	1	140	Mean Difference (IV, Random, 95% CI)	-1.6 [0.00, -1.20]

13.6 Week 12, 80 mg e.w.	1	142	Mean Difference (IV, Random, 95% CI)	-1.5 [-1.88, -1.12]
13.7 Week 26, 20 mg e.w.	1	222	Mean Difference (IV, Random, 95% CI)	-0.90 [-1.30, -0.50]
13.8 Week 26, 20 mg e.o.	1	216	Mean Difference (IV, Random, 95% CI)	-0.60 [-0.99, -0.21]
week				
13.9 Week 26, 40 mg e. week	1	213	Mean Difference (IV, Random, 95% CI)	-1.3 [-1.69, -0.91]
13.10 Week 26, 40 mg e.o.	1	223	Mean Difference (IV, Random, 95% CI)	-1.0 [-1.38, -0.62]
week				
14 Tender joints	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 Week 2, 20 mg e.week	1	141	Mean Difference (IV, Random, 95% CI)	-6.7 [-10.20, -3.20]
14.2 Week 2, 40 mg e.week	1	140	Mean Difference (IV, Random, 95% CI)	-8.5 [-11.95, -5.05]
14.3 Week 2, 80 mg e. week	1	142	Mean Difference (IV, Random, 95% CI)	-10.4 [-14.04, -6.76]
14.4 Week 12, 20 mg e. w.	1	141	Mean Difference (IV, Random, 95% CI)	-8.9 [-14.21, -3.59]
14.5 Week 12, 40 mg, e.w.	1	140	Mean Difference (IV, Random, 95% CI)	-10.20 [-15.18, -5. 22]
14.6 Week 12, 80 mg e.w.	1	142	Mean Difference (IV, Random, 95% CI)	-10.1 [-15.15, -5.05]
14.7 Week 26, 20 mg e.w.	1	222	Mean Difference (IV, Random, 95% CI)	-8.3 [-12.55, -4.05]
14.8 Week 26, 20 mg e.o.	1	216	Mean Difference (IV, Random, 95% CI)	-4.6 [-8.80, -0.40]
week				
14.9 Week 26, 40 mg e. week	1	213	Mean Difference (IV, Random, 95% CI)	-10.50 [-14.81, -6. 19]
14.10 Week 26, 40 mg e.o.	1	223	Mean Difference (IV, Random, 95% CI)	-7.0 [-11.64, -2.36]
week				
15 Swollen joints	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
15.1 Week 2, 20 mg e.week	1	141	Mean Difference (IV, Random, 95% CI)	-3.70 [-5.74, -1.66]
15.2 Week 2, 40 mg e.week	1	140	Mean Difference (IV, Random, 95% CI)	-4.1 [-5.93, -2.27]
15.3 Week 2, 80 mg e. week	1	142	Mean Difference (IV, Random, 95% CI)	-4.5 [-6.61, -2.39]
15.4 Week 12, 20 mg e. w.	1	141	Mean Difference (IV, Random, 95% CI)	-5.3 [-7.86, -2.74]
15.5 Week 12, 40 mg, e.w.	1	140	Mean Difference (IV, Random, 95% CI)	-6.8 [-9.19, -4.41]
15.6 Week 12, 80 mg e.w.	1	142	Mean Difference (IV, Random, 95% CI)	-7.90 [-10.33, -5.47]
15.7 Week 26, 20 mg e.w.	1	222	Mean Difference (IV, Random, 95% CI)	-4.80 [-7.50, -2.10]
15.8 Week 26, 20 mg e.o.	1	216	Mean Difference (IV, Random, 95% CI)	-3.30 [-5.97, -0.63]
week				
15.9 Week 26, 40 mg e. week	1	213	Mean Difference (IV, Random, 95% CI)	-5.9 [-8.64, -3.16]
15.10 Week 26, 40 mg e.o. week	1	223	Mean Difference (IV, Random, 95% CI)	-6.1 [-8.74, -3.46]
16 Patient pain assessment	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1 Week 2, 20 mg e.week	1	141	Mean Difference (IV, Random, 95% CI)	-24.1 [-32.16, -16.
70.1 Week 2, 20 mg e. week	•	111	rican Emerence (14, random, 7574 Oi)	04]
16.2 Week 2, 40 mg e.week	1	140	Mean Difference (IV, Random, 95% CI)	-24.3 [-32.20, -16. 40]
16.3 Week 2, 80 mg e. week	1	142	Mean Difference (IV, Random, 95% CI)	-24.5 [-31.60, -17. 40]
16.4 Week 12, 20 mg e. w.	1	141	Mean Difference (IV, Random, 95% CI)	-24.0 [-33.18, -14. 82]
16.5 Week 12, 40 mg, e.w.	1	140	Mean Difference (IV, Random, 95% CI)	-27.50 [-36.84, -18. 16]
16.6 Week 12, 80 mg e.w.	1	142	Mean Difference (IV, Random, 95% CI)	-22.3 [-30.41, -14. 19]
16.7 Week 26, 20 mg e.w.	1	222	Mean Difference (IV, Random, 95% CI)	-14.2 [-21.78, -6.62]
16.8 Week 26, 20 mg e.o.	1	216	Mean Difference (IV, Random, 95% CI)	-9.10 [-16.73, -1.47]
week			(),(),(),	[

16.9 Week 26, 40 mg e. week	1	213	Mean Difference (IV, Random, 95% CI)	-21.0 [-28.84, -13. 16]
16.10 Week 26, 40 mg e.o. week	1	223	Mean Difference (IV, Random, 95% CI)	-16.6 [-24.20, -7.00]
	2		M D:0 (IV D 1 050/ CI)	C 1 1 1
17 Patient global assessment	2	1/1	Mean Difference (IV, Random, 95% CI)	Subtotals only
17.1 Week 2, 20 mg e.week	1	141	Mean Difference (IV, Random, 95% CI)	-22.9 [-30.60, -15.
17 0 W 1 0 /0		1/0	M Diff (MAD 1 off) (D)	20]
17.2 Week 2, 40 mg e.week	1	140	Mean Difference (IV, Random, 95% CI)	-25.3 [-33.73, -16.
17.2 W. 1.2.00		1/2	M D'M (MAD 1 050/ CD)	87]
17.3 Week 2, 80 mg e. week	1	142	Mean Difference (IV, Random, 95% CI)	-25.5 [-32.53, -18.
47 (W. 1.40.00			II DIM (III D. 1 OFFICE)	47]
17.4 Week 12, 20 mg e. w.	1	141	Mean Difference (IV, Random, 95% CI)	-24.80 [-33.72, -15.
17.5 W. 1.10. /0		1/0	M D'M (MAD 1 050/ CD)	88]
17.5 Week 12, 40 mg, e.w.	1	140	Mean Difference (IV, Random, 95% CI)	-30.70 [-39.63, -21.
47 (W. 1 42 00		1 / 2	MARIA (MARIA A CON)	77]
17.6 Week 12, 80 mg e.w.	1	142	Mean Difference (IV, Random, 95% CI)	-24.10 [-32.29, -15.
17.7 W1-26, 20	1	222	M D:ff (IV D1 050/ CI)	91]
17.7 Week 26, 20 mg e.w.	1	222	Mean Difference (IV, Random, 95% CI)	-15.9 [-23.73, -8.07]
17.8 Week 26, 20 mg e.o. week	1	216	Mean Difference (IV, Random, 95% CI)	-8.9 [-16.61, -1.19]
	1	212	M D'ff (IVD 1 050/CI)	24 4 [22 40 16
17.9 Week 26, 40 mg e. week	1	213	Mean Difference (IV, Random, 95% CI)	-24.4 [-32.40, -16. 40]
17.10 W. 1.26 40	1	222	Mean Difference (IV, Random, 95% CI)	-17.30 [-24.96, -9.
17.10 Week 26, 40 mg e.o. week	1	223	Mean Difference (IV, Kandom, 95% CI)	-1/.30 [-24.96, -9. 64]
18 Physician global assessment	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
18.1 Week 2, 20 mg e.week	1	141	Mean Difference (IV, Random, 95% CI)	-17.3 [-23.46, -11.
16.1 week 2, 20 mg e.week	1	141	Mean Difference (17, Random, 95% CI)	14]
18.2 Week 2, 40 mg e.week	1	140	Mean Difference (IV, Random, 95% CI)	-18.4 [-25.26, -11.
10.2 week 2, 40 mg c.week	1	140	Wear Difference (17, Random, 77/0 Ci)	54]
18.3 Week 2, 80 mg e. week	1	142	Mean Difference (IV, Random, 95% CI)	-20.00 [-28.39, -15.
10.5 week 2, 00 mg c. week	1	1 12	ivican Directive (17, Italiaoni, 7570 Ci)	61]
18.4 Week 12, 20 mg e. w.	1	141	Mean Difference (IV, Random, 95% CI)	-23.8 [-31.28, -16.
10.1 Week 12, 20 mg et m	-		17. cm. 2 11. cm. (1 1, 1 m. 14. cm, 75 70 Cm)	32]
18.5 Week 12, 40 mg, e.w.	1	140	Mean Difference (IV, Random, 95% CI)	-30.70 [-37.71, -23.
1019 Week 12, 10 mg, 0	-	110	17. cm. 2 11. cm. (1 1, 1 m. 14. cm, 75 70 Cm)	69]
18.6 Week 12, 80 mg e.w.	1	142	Mean Difference (IV, Random, 95% CI)	-28.4 [-35.49, -21.
	_			31]
18.7 Week 26, 20 mg e.w.	1	222	Mean Difference (IV, Random, 95% CI)	-15.50 [-22.64, -8.
				36]
18.8 Week 26, 20 mg e.o.	1	216	Mean Difference (IV, Random, 95% CI)	-9.6 [-16.60, -2.60]
week			, , , , ,,	, [
18.9 Week 26, 40 mg e. week	1	213	Mean Difference (IV, Random, 95% CI)	-21.6 [-28.69, -14.
			, , , , , , , , , , , , , , , , , , , ,	51]
18.10 Week 26, 40 mg e.o.	1	223	Mean Difference (IV, Random, 95% CI)	-16.4 [-23.52, -9.28]
week			, , , , , , , , , , , , , , , , , , , ,	
19 HAQ	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
19.1 Week 2, 20 mg e.week	1	141	Mean Difference (IV, Random, 95% CI)	-0.39 [-0.52, -0.26]
19.2 Week 2, 40 mg e.week	1	140	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.45, -0.21]
19.3 Week 2, 80 mg e. week	1	142	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.49, -0.21]
19.4 Week 12, 20 mg e. w.	1	141	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.55, -0.27]
19.5 Week 12, 40 mg, e.w.	1	140	Mean Difference (IV, Random, 95% CI)	-0.43 [-0.56, -0.30]

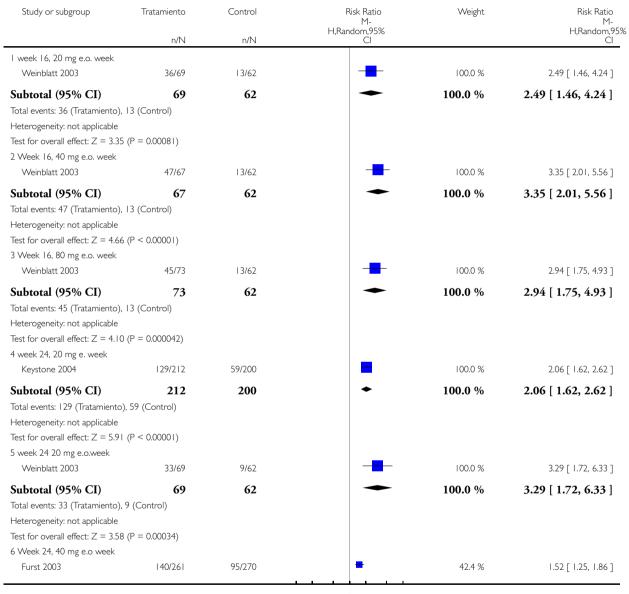
19.6 Week 12, 80 mg e.w.	1	142	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.58, -0.30]
19.7 Week 26, 20 mg e.w.	1	222	Mean Difference (IV, Random, 95% CI)	-0.32 [-0.47, -0.17]
19.8 Week 26, 20 mg e.o.	1	216	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.37, -0.07]
week				
19.9 Week 26, 40 mg e. week	1	213	Mean Difference (IV, Random, 95% CI)	-0.42 [-0.56, -0.28]
19.10 Week 26, 40 mg e.o.	1	223	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.45, -0.17]
week				
20 ESR	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
20.1 Week 2, 20 mg e.week	1	141	Mean Difference (IV, Random, 95% CI)	-17.3 [-23.52, -11.
				08]
20.2 Week 2, 40 mg e.week	1	140	Mean Difference (IV, Random, 95% CI)	-16.8 [-22.57, -11.
-				03]
20.3 Week 2, 80 mg e.week	1	142	Mean Difference (IV, Random, 95% CI)	-18.2 [-23.93, -12.
				47]
20.4 Week 12, 20 mg e. week	1	141	Mean Difference (IV, Random, 95% CI)	-12.2 [-19.12, -5.28]
20.5 Week 12, 40 mg e. w.	1	140	Mean Difference (IV, Random, 95% CI)	-15.90 [-22.54, -9.
				26]
20.6 Week 12, 80 mg, e.w.	1	142	Mean Difference (IV, Random, 95% CI)	-15.30 [-21.99, -8.
				61]
21 CRP	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 Week 2, 20 mg e.week	1	141	Mean Difference (IV, Random, 95% CI)	-28.0 [-40.58, -15.
				42]
21.2 Week 2, 40 mg e. week	1	140	Mean Difference (IV, Random, 95% CI)	-27.0 [-37.80, -16.
				20]
21.3 Week 12, 80 mg e. w.	1	142	Mean Difference (IV, Random, 95% CI)	-33.0 [-46.06, -19.
				94]
21.4 Week 12, 20 mg, e.w.	1	141	Mean Difference (IV, Random, 95% CI)	-23.0 [-24.07, -21.
				93]
21.5 Week 12, 40 mg e.w.	1	140	Mean Difference (IV, Random, 95% CI)	-31.0 [-32.13, -29.
				87]
21.6 Week 26, 80 mg e.w.	1	142	Mean Difference (IV, Random, 95% CI)	-33.0 [-41.12, -24.
-				88]
22 Withdrawals	2	828	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.38, 0.57]

Analysis I.I. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome I ACR 20.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs)

Outcome: I ACR 20



0.1 0.2 0.5 | 2 5 10 Favours control Favours treatment

(Continued ...)

Study or subgroup	Tratamiento n/N	Control n/N	Risk Ratio M- H,Random,95% CI	Weight	(Continued) Risk Ratio M- H,Random,95% Cl
Keystone 2004	131/207	59/200	-	39.7 %	2.15 [1.69, 2.72]
Weinblatt 2003	45/67	9/62		17.9 %	4.63 [2.47, 8.66]
Subtotal (95% CI)	535	532	•	100.0 %	2.24 [1.43, 3.52]
Total events: 316 (Tratamiento Heterogeneity: Tau ² = 0.12; C Test for overall effect: $Z = 3.5$: 7 Week 24, 80 mg e.o. week	$hi^2 = 13.73$, df = 2 (P =	= 0.001); I ² =85%			
Weinblatt 2003	48/73	9/62	-	100.0 %	4.53 [2.42, 8.47]
Subtotal (95% CI)	73	62	-	100.0 %	4.53 [2.42, 8.47]
Total events: 48 (Tratamiento), Heterogeneity: not applicable Test for overall effect: $Z = 4.72$ 8 Week 52, 20 mg e. week	3 (P < 0.00001)	40.000		10000	2005172 2003
Keystone 2004	116/212	48/200	_	100.0 %	2.28 [1.73, 3.00]
Subtotal (95% CI) Total events: 116 (Tratamiento Heterogeneity: not applicable Test for overall effect: Z = 5.87 9 Week 52, 40 mg e.o.week	7 (P < 0.00001)	200		100.0 %	2.28 [1.73, 3.00]
Keystone 2004	122/207	48/200		100.0 %	2.46 [1.87, 3.22]
Subtotal (95% CI) Total events: 122 (Tratamiento Heterogeneity: not applicable Test for overall effect: Z = 6.48		200	•	100.0 %	2.46 [1.87, 3.22]
10 Week 4 (period), 1 mg/kg, Rau 2004	once 12/18	5/18	_	100.0 %	2.40 [1.06, 5.41]
Subtotal (95% CI) Total events: 12 (Tratamiento). Heterogeneity: not applicable Test for overall effect: Z = 2.1	,	18		100.0 %	2.40 [1.06, 5.41]

0.1 0.2 0.5 1 2 5 10

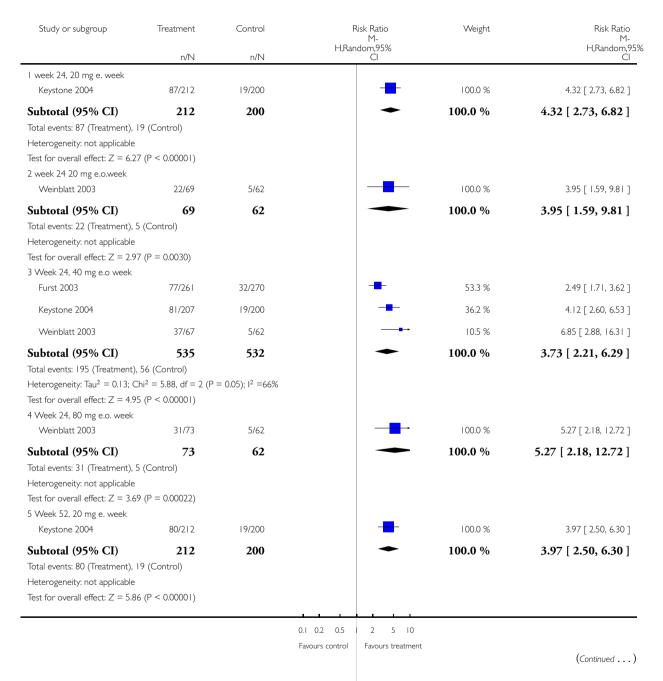
Favours control Favours treatment

Analysis I.2. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 2 ACR50.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs)

Outcome: 2 ACR50



Adalimumab for treating rheumatoid arthritis (Review)

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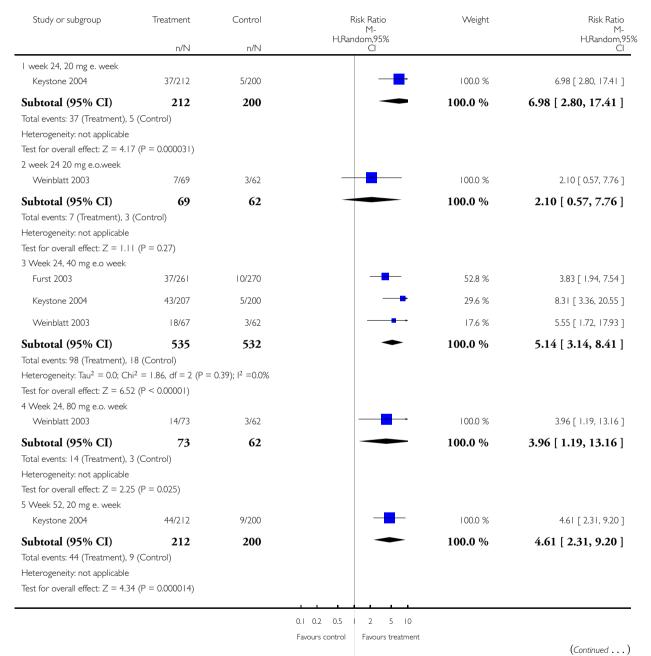
Study or subgroup	Treatment	Control	F	Risk Ratio M-	Weight	(Continued) Risk Ratio M-	
	n/N	n/N	H,Rar	ndom,95% Cl		H,Random,95% Cl	
6 Week 52, 40 mg e.o.week							
Keystone 2004	86/207	19/200		-	100.0 %	4.37 [2.77, 6.91]	
Subtotal (95% CI)	207	200		•	100.0 %	4.37 [2.77, 6.91]	
Total events: 86 (Treatment),	19 (Control)						
Heterogeneity: not applicable							
Test for overall effect: $Z = 6.3$	32 (P < 0.00001)						
7 Week 4 (period) I mg/kg, o	once						
Rau 2004	3/18	0/18		-	100.0 %	7.00 [0.39, 126.48]	
Subtotal (95% CI)	18	18			100.0 %	7.00 [0.39, 126.48]	
Total events: 3 (Treatment), 0	(Control)						
Heterogeneity: not applicable							
Test for overall effect: $Z = 1.3$	32 (P = 0.19)						
			0.1 0.2 0.5	1 2 5 10			

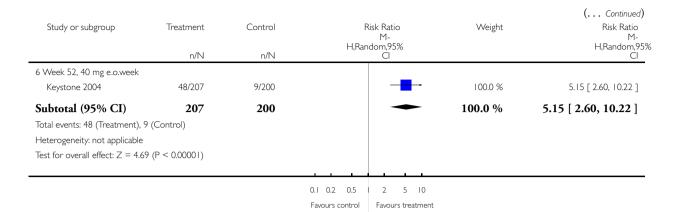
Analysis 1.3. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 3 ACR70.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs)

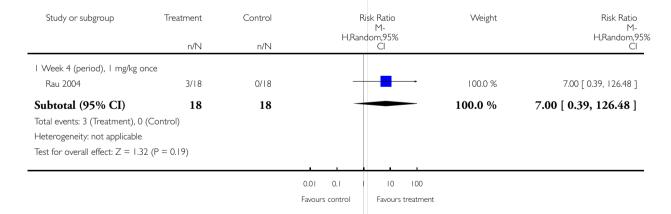
Outcome: 3 ACR70





Analysis I.4. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs),
Outcome 4 EULAR response good.



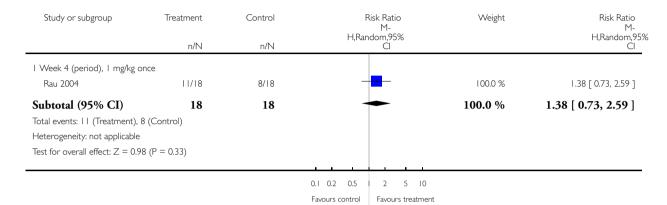


Analysis I.5. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 5 EULAR response moderate.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c +MTX (or DMARDs)

Outcome: 5 EULAR response moderate

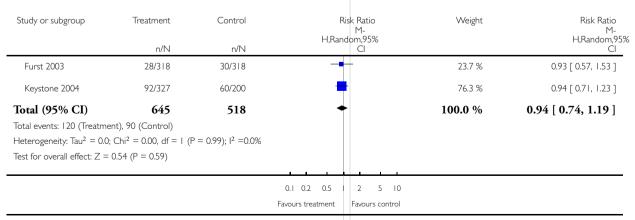


Analysis I.6. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs),
Outcome 6 Withdrawals.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs)

Outcome: 6 Withdrawals



Adalimumab for treating rheumatoid arthritis (Review)

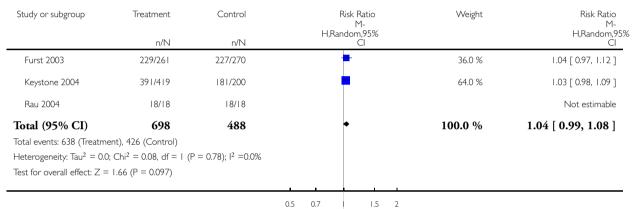
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Analysis 1.7. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 7 Adverse events (all doses of adalimumab).

Review: Adalimumab for treating rheumatoid arthritis

 ${\it Comparison:} \quad {\it I \ Adalimumab \ s.c + MTX \ (or \ DMARDs) \ versus \ Placebo \ s.c + MTX \ (or \ DMARDs)}$

Outcome: 7 Adverse events (all doses of adalimumab)



0.5 0.7 Favours treatment

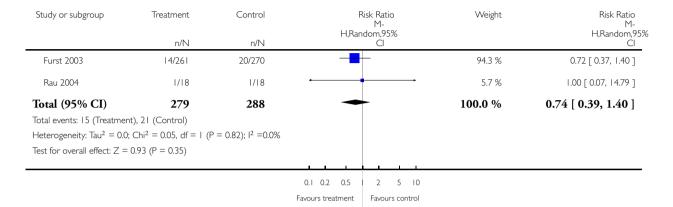
Favours control

Analysis I.8. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 8 Serious adverse events (all doses of Adalimumab).

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs)

Outcome: 8 Serious adverse events (all doses of Adalimumab)



Analysis I.9. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs),
Outcome 9 Withdrawals due to adverse events (all doses of adalimumab).

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs)

Outcome: 9 Withdrawals due to adverse events (all doses of adalimumab)

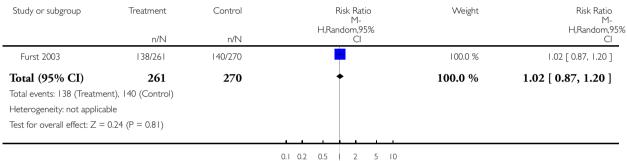
Study or subgroup	Treatment	Control		Risk Ratio M- ndom,95%	Weight	Risk Ratio M- H,Random,95%
	n/N	n/N	1 1,1 (4.1	Cl		Cl
Furst 2003	7/261	6/270		-	21.4 %	1.21 [0.41, 3.54]
Keystone 2004	42/419	13/200	-	-	69.1 %	1.54 [0.85, 2.81]
Rau 2004	0/18	0/18				Not estimable
Weinblatt 2003	5/209	2/62			9.5 %	0.74 [0.15, 3.73]
Total (95% CI)	907	550	-	•	100.0 %	1.37 [0.83, 2.25]
Total events: 54 (Treatme	nt), 21 (Control)					
Heterogeneity: Tau ² = 0.0	0; $Chi^2 = 0.76$, $df = 2$ (F	$P = 0.68$); $I^2 = 0.0\%$				
Test for overall effect: Z =	= 1.23 (P = 0.22)					
			0.1 0.2 0.5	2 5 10		
			Favours treatment	Favours control		

Analysis 1.10. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 10 Infections (all doses of adalimumab).

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs)

Outcome: 10 Infections (all doses of adalimumab)



Favours treatment Favours control

Analysis I.II. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome II Serious infections (all doses of Adalimumab).

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c +MTX (or DMARDs)

Outcome: II Serious infections (all doses of Adalimumab)

Study or subgroup	Treatment	Control	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Furst 2003	4/261	6/270			0.69 [0.20, 2.42]
Keystone 2004	16/419	1/200			7.64 [1.02, 57.18]
Rau 2004	0/18	0/18			Not estimable
Subtotal (95% CI)	0	0			0.0 [0.0, 0.0]
Total events: 20 (Treatment), 7	(Control)				
Heterogeneity: Tau ² = 0.0; Chi	$i^2 = 0.0$, df = 0 (P<0.000	001); I ² =0.0%			
Test for overall effect: $Z = 0.0$	(P < 0.00001)				
-					
			0.00000		

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

Analysis 1.12. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 12 Tender joints.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c +MTX (or DMARDs)

Outcome: 12 Tender joints

Study or subgroup	Treatment		Control		Mean Difference	Weight	Mean Difference	
, , ,	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI	-	IV,Random,95% CI	
I Week 24, 20 mg e. week								
Keystone 2004	212	-16.6 (12)	200	-9.3 (14.4)	•	100.0 %	-7.30 [-9.87, -4.73]	
Subtotal (95% CI)	212		200		•	100.0 %	-7.30 [-9.87, -4.73]	
Heterogeneity: not applicat	ole							
Test for overall effect: $Z = \frac{1}{2}$	5.57 (P < 0.00	0001)						
2 Week 24, 20 mge.o. wee	k							
Weinblatt 2003	69	-14.4 (15.1)	62	-5.3 (12.1)	-	100.0 %	-9.10 [-13.77, -4.43]	
Subtotal (95% CI)	69		62		•	100.0 %	-9.10 [-13.77, -4.43]	
Heterogeneity: not applicab	ole							
Test for overall effect: $Z = \frac{1}{2}$	3.82 (P = 0.00	0013)						
3 Week 24, 40 mg e.o. wee	ek							
Keystone 2004	207	-15.4 (12.3)	200	-9.3 (14.4)	•	80.7 %	-6.10 [-8.71, -3.49]	
Weinblatt 2003	67	-14.4 (18.4)	62	-5.3 (12.1)	-	19.3 %	-9.10 [-14.44, -3.76]	
Subtotal (95% CI)	274		262		•	100.0 %	-6.68 [-9.02, -4.34]	
Heterogeneity: Tau ² = 0.0;	$Chi^2 = 0.98, c$	df = I (P = 0.32)	; I ² =0.0%					
Test for overall effect: $Z = $	5.59 (P < 0.00	0001)						
4 week 24, 80 mg e.o weel	<							
Weinblatt 2003	73	-16.8 (13.8)	62	-5.3 (12.1)	-	100.0 %	-11.50 [-15.87, -7.13]	
Subtotal (95% CI)	73		62		•	100.0 %	-11.50 [-15.87, -7.13]	
Heterogeneity: not applicab	ole							
Test for overall effect: $Z = \frac{1}{2}$	5.16 (P < 0.00	0001)						
5 Week 52, 20 mg e. week								
Keystone 2004	212	-16.8 (13.8)	200	-9.6 (14.7)	•	100.0 %	-7.20 [-9.96, -4.44]	
Subtotal (95% CI)	212		200		•	100.0 %	-7.20 [-9.96, -4.44]	
Heterogeneity: not applicab	ole							
Test for overall effect: $Z = \frac{1}{2}$	5.12 (P < 0.00	0001)						
6 Week 52, 40 mg e.o. wee	ek							
Keystone 2004	207	-16.6 (12.8)	200	-9.6 (14.7)	+	100.0 %	-7.00 [-9.68, -4.32]	
Subtotal (95% CI)	207		200		•	100.0 %	-7.00 [-9.68, -4.32]	
Heterogeneity: not applicat	ole							
Test for overall effect: $Z = \frac{1}{2}$	5.12 (P < 0.00	0001)						

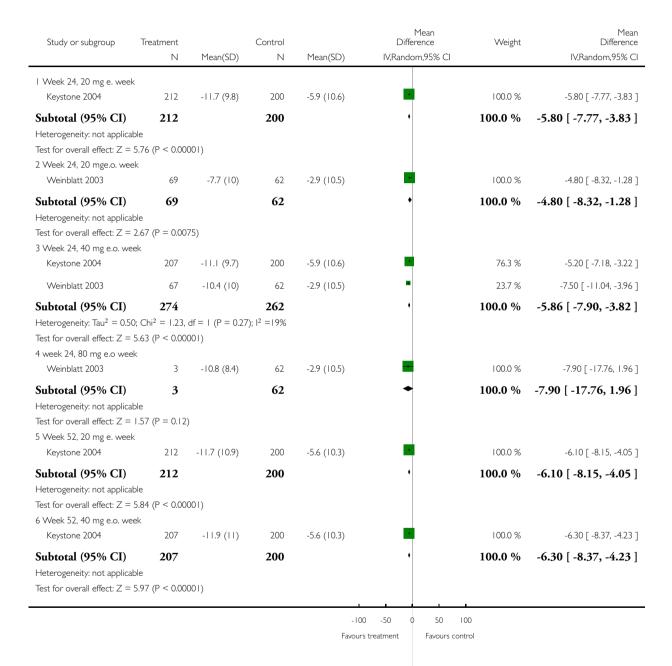
-100 -50 0 50 100
Favours treatment Favours control

Analysis 1.13. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 13 Swollen joints.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs)

Outcome: 13 Swollen joints



Analysis 1.14. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 14 Patient pain assessment.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c +MTX (or DMARDs)

Outcome: 14 Patient pain assessment

Study or subgroup	Treatment		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
I Week 24, 20 mg e. week Keystone 2004	212	-27.9 (27)	200	-12.6 (26.1)	-	100.0 %	-15.30 [-20.43, -10.17]
Subtotal (95% CI)	212		200		•	100.0 %	-15.30 [-20.43, -10.17]
Heterogeneity: not applical	ble						
Test for overall effect: $Z =$	`	0001)					
2 Week 24, 20 mge.o. wee Weinblatt 2003	ek 69	-24.8 (24.2)	62	-8.6 (22.5)	_	100.0 %	-16.20 [-24.20, -8.20]
		-24.8 (24.2)		-8.6 (22.5)	_		
Subtotal (95% CI)	69		62		•	100.0 %	-16.20 [-24.20, -8.20]
Heterogeneity: not applical Test for overall effect: Z =		10072)					
3 Week 24, 40 mg e.o. we	`	50072)					
Keystone 2004	207	-28.2 (25.8)	200	-12.6 (26.1)		78.7 %	-15.60 [-20.64, -10.56]
Weinblatt 2003	67	-25.1 (33.1)	62	-8.6 (22.5)	-	21.3 %	-16.50 [-26.20, -6.80]
Subtotal (95% CI)	274		262		•	100.0 %	-15.79 [-20.27, -11.32]
Heterogeneity: $Tau^2 = 0.0$; Test for overall effect: $Z =$ 4 week 24, 80 mg e.o week	6.92 (P < 0.0	`); I ² =0.0%				
Weinblatt 2003	73	-27.6 (24.7)	62	-8.6 (22.5)	-	100.0 %	-19.00 [-26.97, -11.03]
Subtotal (95% CI) Heterogeneity: not applical Test for overall effect: Z = 5 Week 52, 20 mg e. week	4.67 (P < 0.00	0001)	62		•	100.0 %	-19.00 [-26.97, -11.03]
Keystone 2004	212	-27.4 (28.5)	200	-11.2 (27.7)	-	100.0 %	-16.20 [-21.63, -10.77]
Subtotal (95% CI)	212		200		•	100.0 %	-16.20 [-21.63, -10.77]
Heterogeneity: not applical	ble						
Test for overall effect: $Z =$	5.85 (P < 0.0	0001)					
6 Week 52, 40 mg e.o. we							
Keystone 2004	207	-29.4 (26.4)	200	-11.2 (27.7)	-	100.0 %	-18.20 [-23.46, -12.94]
Subtotal (95% CI) Heterogeneity: not applical Test for overall effect: Z =		0001)	200		•	100.0 %	-18.20 [-23.46, -12.94]
				-100) -50 0 50 I	00	

Favours control

Favours treatment

Analysis 1.15. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 15 Patient global assessment.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c +MTX (or DMARDs)

Outcome: 15 Patient global assessment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
I Week 24, 20 mg e. week	212	247 (272)	200	11.4 (20.1)	_	100000	1220 5 10 (5 705 7
Keystone 2004	212	-24.7 (27.2)	200	-11.4 (28.1)	•	100.0 %	-13.30 [-18.65, -7.95]
Subtotal (95% CI)	212		200		•	100.0 %	-13.30 [-18.65, -7.95]
Heterogeneity: not applicab							
Test for overall effect: $Z = 4$	`	0001)					
2 Week 24, 20 mge.o. week Weinblatt 2003	69	-27.1 (24.6)	62	0 4 (25 1)	_	100.0 %	10501 2702 0071
		-27.1 (24.0)		-8.6 (25.1)	-		-18.50 [-27.03, -9.97]
Subtotal (95% CI)	69		62		•	100.0 %	-18.50 [-27.03, -9.97]
Heterogeneity: not applicab		00001)					
Test for overall effect: $Z = 4$	`	00021)					
3 Week 24, 40 mg e.o. wee Keystone 2004	к 207	-27.2 (26.9)	200	-11.4 (28.1)	_	76.8 %	-15.80 [-21.15, -10.45]
,		` /		` '	_		
Weinblatt 2003	67	-29.7 (31.8)	62	-8.6 (25.1)	-	23.2 %	-21.10 [-30.95, -11.25]
Subtotal (95% CI)	274		262		•	100.0 %	-17.01 [-21.71, -12.31]
Heterogeneity: $Tau^2 = 0.0$; ($Chi^2 = 0.86,$	df = 1 (P = 0.35)	$5); I^2 = 0.0\%$				
Test for overall effect: $Z = 7$	'.09 (P < 0.0	0001)					
4 week 24, 80 mg e.o week					_		
Weinblatt 2003	73	-32 (25.9)	62	-8.6 (25.1)	-	100.0 %	-23.40 [-32.02, -14.78]
Subtotal (95% CI)	73		62		•	100.0 %	-23.40 [-32.02, -14.78]
Heterogeneity: not applicab	le						
Test for overall effect: $Z = 5$.32 (P < 0.0	0001)					
5 Week 52, 20 mg e. week					_		
Keystone 2004	212	-24.1 (28.4)	200	-10.9 (30.4)	-	100.0 %	-13.20 [-18.89, -7.51]
Subtotal (95% CI)	212		200		•	100.0 %	-13.20 [-18.89, -7.51]
Heterogeneity: not applicab	le						
Test for overall effect: $Z = 4$	`	0001)					
6 Week 52, 40 mg e.o. wee							
Keystone 2004	207	-27.5 (28.4)	200	-10.9 (30.4)	•	100.0 %	-16.60 [-22.32, -10.88]
Subtotal (95% CI)	207		200		•	100.0 %	-16.60 [-22.32, -10.88]
Heterogeneity: not applicab							
Test for overall effect: $Z = 5$.69 (P < 0.0	0001)					
					20 50 50	00	
				-1(Favou	00 -50 0 50 I	00	
				1°dVOU	1 avour's Con	iu Oi	

Analysis 1.16. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 16 Physician global assessment.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c +MTX (or DMARDs)

Outcome: 16 Physician global assessment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
I Week 24, 20 mg e. week	(_		
Keystone 2004	212	-36.3 (24.1)	200	-21.1 (25.3)	-	100.0 %	-15.20 [-19.98, -10.42]
Subtotal (95% CI)	212		200		•	100.0 %	-15.20 [-19.98, -10.42]
Heterogeneity: not applical	ole						
Test for overall effect: Z =	`	0001)					
2 Week 24, 20 mge.o. wee		20.2 (22.4)	(2	(0 (0 4 5)		100000	22505 2170 1540 3
Weinblatt 2003	69	-30.3 (22.6)	62	-6.8 (24.5)	_	100.0 %	-23.50 [-31.60, -15.40]
Subtotal (95% CI)	69		62		•	100.0 %	-23.50 [-31.60, -15.40]
Heterogeneity: not applical							
Test for overall effect: $Z = 3$ Week 24, 40 mg e.o. we	`	0001)					
Keystone 2004	ek 207	-37.3 (21.6)	200	-21.1 (25.3)	•	62.5 %	-16.20 [-20.78, -11.62]
Weinblatt 2003	67	-31.1 (24.9)	62	-6.8 (24.5)	-	37.5 %	-24.30 [-32.83, -15.77]
Subtotal (95% CI)	274		262		•	100.0 %	-19.42 [-27.19, -11.65]
Heterogeneity: Tau ² = 20.6	61; Chi ² = 2.6	9, $df = 1 (P = 0.$	10); I ² =63	%			
Test for overall effect: Z =	4.90 (P < 0.00	0001)					
4 week 24, 80 mg e.o wee	k				_		
Weinblatt 2003	73	-38 (22.6)	62	-6.8 (24.5)	-	100.0 %	-31.20 [-39.20, -23.20]
Subtotal (95% CI)	73		62		•	100.0 %	-31.20 [-39.20, -23.20]
Heterogeneity: not applical	ole						
Test for overall effect: Z =	`	0001)					
5 Week 52, 20 mg e. week		2/2/2/	200	10.5 (25.0)	_	100000	1/70 5 21 5/ 11 24 7
Keystone 2004	212	-36.2 (24.4)	200	-19.5 (25.8)	-	100.0 %	-16.70 [-21.56, -11.84]
Subtotal (95% CI)	212		200		•	100.0 %	-16.70 [-21.56, -11.84]
Heterogeneity: not applical		2001)					
Test for overall effect: $Z = 6$ Week 52, 40 mg e.o. we	`	0001)					
Keystone 2004	ek 207	-39.4 (22.2)	200	-19.5 (25.8)	-	100.0 %	-19.90 [-24.58, -15.22]
Subtotal (95% CI)	207		200		•	100.0 %	-19.90 [-24.58, -15.22]
Heterogeneity: not applical	ole						
Test for overall effect: $Z =$	8.33 (P < 0.00	0001)					
				-10		00	
				Favour	s treatment Favours con	trol	

Analysis 1.17. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 17 HAQ.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c +MTX (or DMARDs)

Outcome: 17 HAQ

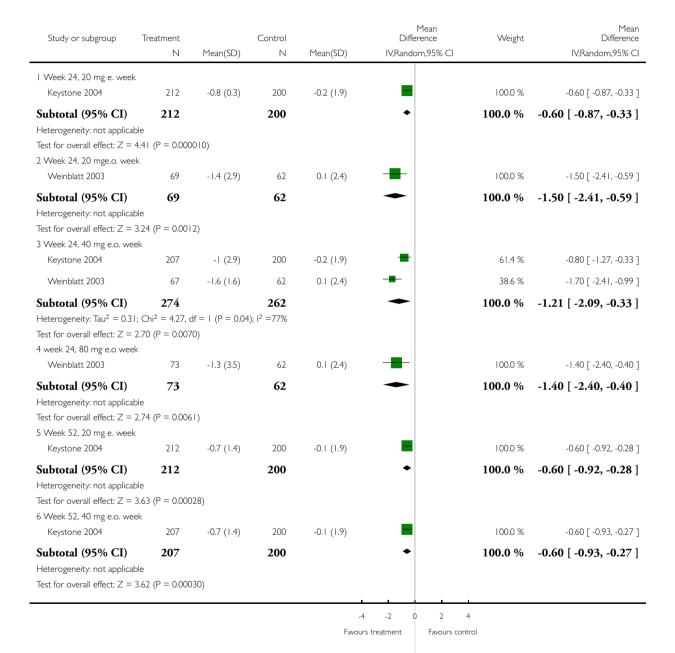
Study or subgroup	Treatment		Control		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
I Week 24, 20 mg e. week							
Keystone 2004	212	-0.6 (0.53)	200	-0.24 (0.52)	-	100.0 %	-0.36 [-0.46, -0.26]
Subtotal (95% CI)	212		200		•	100.0 %	-0.36 [-0.46, -0.26]
Heterogeneity: not applicable	e						
Test for overall effect: $Z = 6.9$	96 (P < 0.00	001)					
2 Week 24, 20 mge.o. week					_		
Weinblatt 2003	69	-0.54 (0.58)	62	-0.27 (0.57)	-	100.0 %	-0.27 [-0.47, -0.07]
Subtotal (95% CI)	69		62		•	100.0 %	-0.27 [-0.47, -0.07]
Heterogeneity: not applicable	9						
Test for overall effect: $Z = 2.6$	`	73)					
3 Week 24, 40 mg e.o. week					_		
Keystone 2004	207	-0.56 (0.52)	200	-0.24 (0.52)	-	80.8 %	-0.32 [-0.42, -0.22]
Weinblatt 2003	67	-0.62 (0.63)	62	-0.27 (0.57)		19.2 %	-0.35 [-0.56, -0.14]
Subtotal (95% CI)	274		262		•	100.0 %	-0.33 [-0.42, -0.23]
Heterogeneity: $Tau^2 = 0.0$; C Test for overall effect: $Z = 7.0$ 4 week 24, 80 mg e.o week	03 (P < 0.00	001)		0.27 (0.57)	_	10000	0221 011 0121
Weinblatt 2003	73	-0.59 (0.53)	62	-0.27 (0.57)	-	100.0 %	-0.32 [-0.51, -0.13]
Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: Z = 3.3		079)	62		•	100.0 %	-0.32 [-0.51, -0.13]
5 Week 52, 20 mg e. week	30 (1 0.00	017)					
Keystone 2004	212	-0.61 (0.55)	200	-0.25 (0.56)	-	100.0 %	-0.36 [-0.47, -0.25]
Subtotal (95% CI)	212		200		•	100.0 %	-0.36 [-0.47, -0.25]
Heterogeneity: not applicable	9						
Test for overall effect: $Z = 6.5$	58 (P < 0.00	001)					
6 Week 52, 40 mg e.o. week	:				_		
Keystone 2004	207	-0.59 (0.57)	200	-0.25 (0.56)	-	100.0 %	-0.34 [-0.45, -0.23]
Subtotal (95% CI)	207		200		•	100.0 %	-0.34 [-0.45, -0.23]
Heterogeneity: not applicable Test for overall effect: $Z = 6.0$		001)					
						1	
				-1	-0.5 0 0.5	I	
				Favour	rs treatment Favours con	trol	

Analysis 1.18. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 18 CRP.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c +MTX (or DMARDs)

Outcome: 18 CRP



Analysis 1.19. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 19 Modified Sharp Index.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c +MTX (or DMARDs)

Outcome: 19 Modified Sharp Index

Study or subgroup	Treatment	Control			Mean Difference	Weight	Mean Difference
	N	Mean(SD)) N Mean(SE		IV,Random,95% CI		IV,Random,95% CI
I Week 52, 20 mg e. weel	k						
Keystone 2004	196	0.8 (4.9)	172	2.7 (6.8)	-	100.0 %	-1.90 [-3.13, -0.67]
Subtotal (95% CI)	196		172		-	100.0 %	-1.90 [-3.13, -0.67]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	3.04 (P = 0.002	24)					
2 Week 52, 40 mg e.o. we	ek						
Keystone 2004	183	0.1 (4.8)	172	2.7 (6.8)		100.0 %	-2.60 [-3.83, -1.37]
Subtotal (95% CI)	183		172		•	100.0 %	-2.60 [-3.83, -1.37]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	4.14 (P = 0.000	0035)					

2 4

Analysis 1.20. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 20 Erosion score.

Review: Adalimumab for treating rheumatoid arthritis

 $Comparison: \quad I \ \ Adalimum ab \ s.c + MTX \ (or \ DMARDs) \ versus \ Placebo \ s.c + MTX \ (or \ DMARDs)$

Outcome: 20 Erosion score

Study or subgroup	Treatment Control				Mean Difference	Weight	Mean Difference	
,	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI	
I Week 52, 20 mg e. week								
Keystone 2004	196	0.4 (2.5)	172	1.6 (4.4)	-	100.0 %	-1.20 [-1.94, -0.46]	
Subtotal (95% CI)	196		172		•	100.0 %	-1.20 [-1.94, -0.46]	
Heterogeneity: not applicab	ole							
Test for overall effect: $Z = 3$	3.16 (P = 0.001	6)						
2 Week 52, 40 mg e.o. wee	ek							
Keystone 2004	183	0 (2.8)	172	1.6 (4.4)	-	100.0 %	-1.60 [-2.37, -0.83]	
Subtotal (95% CI)	183		172		•	100.0 %	-1.60 [-2.37, -0.83]	
Heterogeneity: not applicab	ole							
Test for overall effect: $Z = 4$	4.06 (P = 0.000	049)						

Favours treatment

Favours control

Analysis 1.21. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 21 Joint space index.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs)

Outcome: 21 Joint space index

Study or subgroup	Treatment		Control			Mean rence	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Rando	m,95% CI		IV,Random,95% CI
I Week 52, 40 mg e.o. w	/eek							
Keystone 2004	183	0.1 (2.3)	172	I (3)	-		100.0 %	-0.90 [-1.46, -0.34]
Subtotal (95% CI)	183		172		•		100.0 %	-0.90 [-1.46, -0.34]
Heterogeneity: not applic	able							
Test for overall effect: Z =	= 3.16 (P = 0.001	6)						
							L	
				_4	1 -2 C	2 -	4	
				Favou	rs treatment	Favours conf	trol	

Analysis 1.22. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 22 ANA (all doses of Adalimumab).

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs)

Outcome: 22 ANA (all doses of Adalimumab)

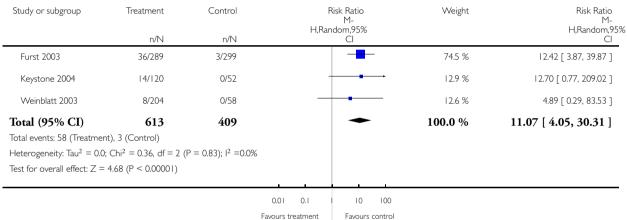
Study or subgroup	Treatment	Control			Risk Ratio M- ndom,95%		Weight	Risk Ratio M- H,Random,95%
	n/N	n/N			Cl			Cl
Furst 2003	66/249	39/256			-		63.8 %	1.74 [1.22, 2.48]
Keystone 2004	48/397	17/186		_	-		29.2 %	1.32 [0.78, 2.24]
Rau 2004	1/18	1/18	-			-	1.1 %	1.00 [0.07, 14.79]
Weinblatt 2003	18/162	3/49				+	5.8 %	1.81 [0.56, 5.90]
Total (95% CI)	826	509			•		100.0 %	1.60 [1.20, 2.13]
Total events: 133 (Treatm	ent), 60 (Control)							
Heterogeneity: Tau ² = 0.0); $Chi^2 = 0.88$, $df = 3$ (P	$= 0.83$); $I^2 = 0.0\%$						
Test for overall effect: Z =	= 3.24 (P = 0.0012)							
			i	ı				
			0.2	0.5	1 2	5		
			Favours t	reatment	Favours co	ntrol		

Analysis I.23. Comparison I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs), Outcome 23 AntiDNA (all doses of adalimumab).

Review: Adalimumab for treating rheumatoid arthritis

Comparison: I Adalimumab s.c + MTX (or DMARDs) versus Placebo s.c + MTX (or DMARDs)

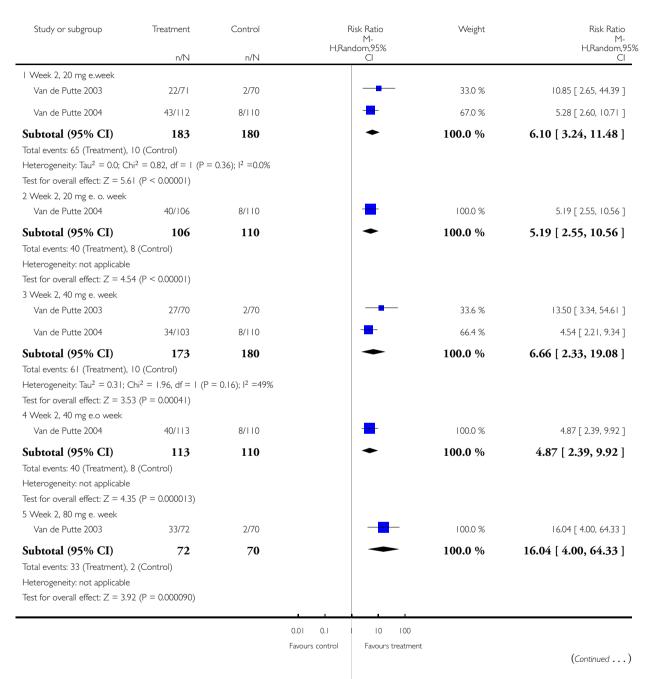
Outcome: 23 AntiDNA (all doses of adalimumab)



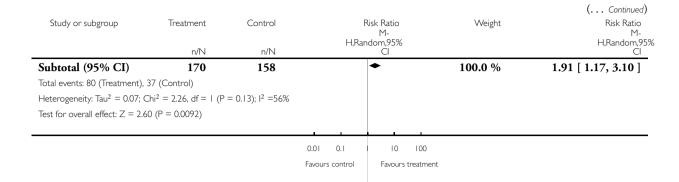
Analysis 2.1. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome I ACR20.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: I ACR20



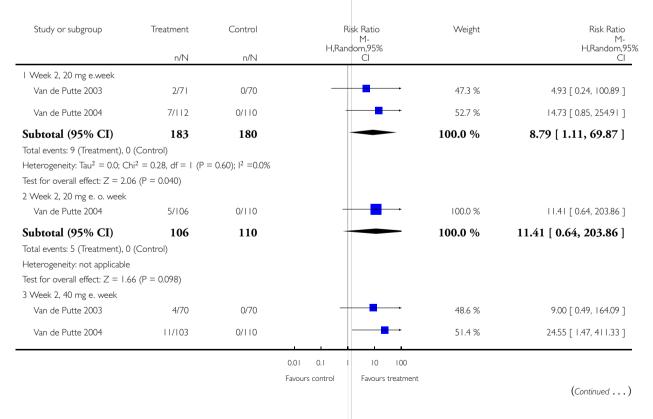
Study or subgroup	Treatment	Control		k Ratio M-	Weight	(Continued) Risk Ratio M-
	n/N	n/N	H,Rando	om,95% Cl		H,Random,959 Cl
6 Week 12, 20 mg e. week Van de Putte 2003	36/71	7/70			100.0 %	5.07 [2.42, 10.62]
Subtotal (95% CI)	71	70		•	100.0 %	5.07 [2.42, 10.62]
Total events: 36 (Treatment), 7	(Control)					
Heterogeneity: not applicable Test for overall effect: $Z = 4.30$ 7 Week 12 40 mg e. week	(P = 0.000017)					
Van de Putte 2003	40/70	7/70		-	100.0 %	5.71 [2.75, 11.88]
Subtotal (95% CI)	70	70		•	100.0 %	5.71 [2.75, 11.88]
Total events: 40 (Treatment), 7 Heterogeneity: not applicable Test for overall effect: Z = 4.67 8 Week 12, 80 mg e. week Van de Putte 2003	, ,	7/70			100.0 %	5.42 [2.60, 11.29]
Subtotal (95% CI)	72	70		•	100.0 %	5.42 [2.60, 11.29]
Total events: 39 (Treatment), 7 Heterogeneity: not applicable Test for overall effect: Z = 4.51 9 Week 24/26, 20 mg e. week Van de Putte 2004	(Control)	21/110		•	100.0 %	2.06 [1.31, 3.22]
Subtotal (95% CI) Total events: 44 (Treatment), 21 Heterogeneity: not applicable Test for overall effect: Z = 3.15	,	110			100.0 %	2.06 [1.31, 3.22]
10 Week 24/26, 20 mg e.o. wee				_		
Van de Putte 2004	38/106	21/110			100.0 %	1.88 [1.18, 2.98]
Subtotal (95% CI) Total events: 38 (Treatment), 21 Heterogeneity: not applicable Test for overall effect: $Z = 2.68$,	110		•	100.0 %	1.88 [1.18, 2.98]
11 Week 24/26, 40 mg e. week				_		
Van de Putte 2004	55/103	21/110			100.0 %	2.80 [1.83, 4.28]
Subtotal (95% CI) Total events: 55 (Treatment), 21 Heterogeneity: not applicable Test for overall effect: $Z = 4.74$,	110		•	100.0 %	2.80 [1.83, 4.28]
12 Week 24/26, 40 mg e.o. wee Furst 2003	ek 28/57	16/48	_	F	49.1 %	1.47 [0.91, 2.38]
Van de Putte 2004	52/113	21/110			50.9 %	2.41 [1.56, 3.72]
van de i dite 2001	<i>52</i> /115	21/110			50.7 /6	2.11 [1.20, 3.72]
			0.01 0.1 Favours control	10 100 Favours treatment		(Continued)

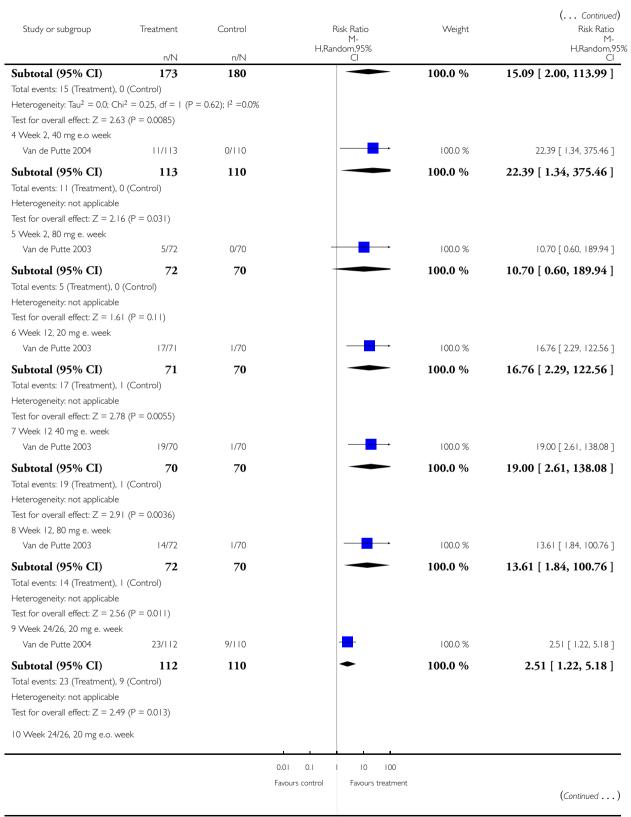


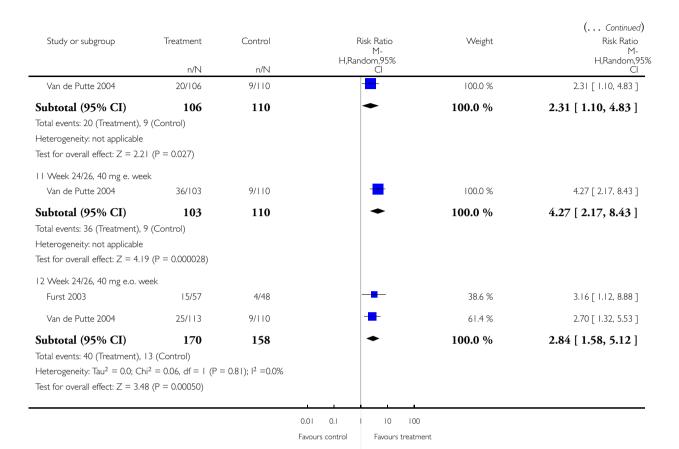
Analysis 2.2. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 2 ACR 50.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 2 ACR 50



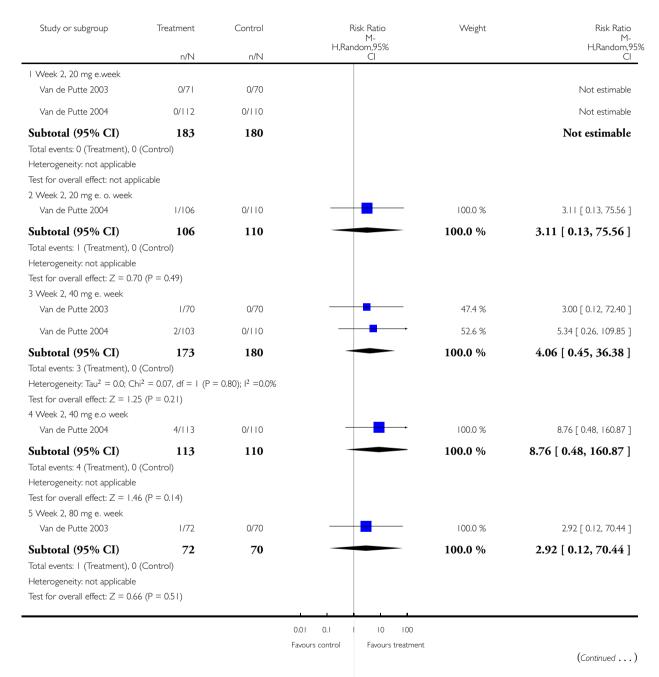




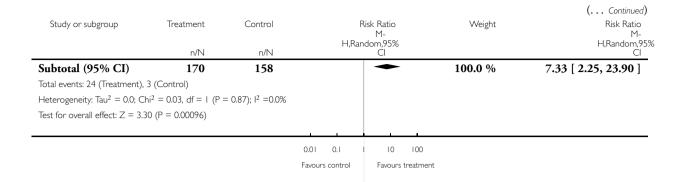
Analysis 2.3. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 3 ACR70.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 3 ACR70







Analysis 2.4. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 4 EULAR response: at least moderate.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 4 EULAR response: at least moderate

Study or subgroup	Treatment	Control		Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Rai	ndom,95% Cl		H,Random,95% Cl
I Week 2, 20 mg e.week						
Van de Putte 2004	54/112	16/110		-	100.0 %	3.31 [2.03, 5.42]
Subtotal (95% CI)	112	110		•	100.0 %	3.31 [2.03, 5.42]
Total events: 54 (Treatment), I	6 (Control)					
Heterogeneity: not applicable						
Test for overall effect: $Z = 4.77$	7 (P < 0.00001)					
2 Week 2, 20 mg e. o. week				_		
Van de Putte 2004	51/106	16/110			100.0 %	3.31 [2.02, 5.42]
Subtotal (95% CI)	106	110		•	100.0 %	3.31 [2.02, 5.42]
Total events: 51 (Treatment), 1	6 (Control)					
Heterogeneity: not applicable						
Test for overall effect: $Z = 4.74$	1 (P < 0.00001)					
3 Week 2, 40 mg e. week				_		
Van de Putte 2004	50/103	16/110		-	100.0 %	3.34 [2.04, 5.47]
Subtotal (95% CI)	103	110		•	100.0 %	3.34 [2.04, 5.47]
			0.1 0.2 0.5	2 5 10		
			Favours control	Favours treatment		(Continued)

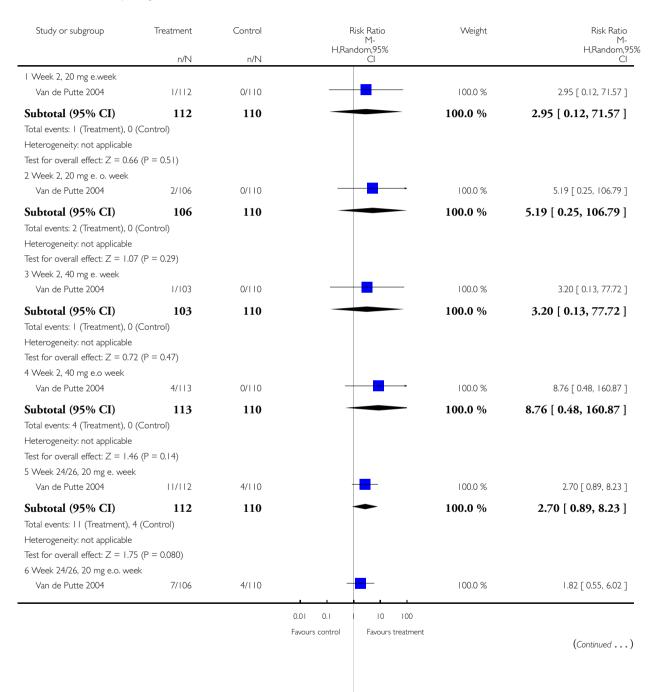
Study or subgroup	Treatment	Control	Risk Ratio M- H,Random <u>,</u> 95%	Weight	(Continued) Risk Ratio M- H,Random <u>,</u> 959
T. I 50/T	n/N	n/N	CI		Cl
Total events: 50 (Treatment), 16	(Control)				
Heterogeneity: not applicable Test for overall effect: $Z = 4.78$ (D < 0.00001)				
4 Week 2, 40 mg e.o week	r < 0.00001)				
Van de Putte 2004	57/113	16/110	-	100.0 %	3.47 [2.13, 5.65]
Subtotal (95% CI)	113	110	•	100.0 %	3.47 [2.13, 5.65]
Total events: 57 (Treatment), 16	(Control)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 4.99$ ((P < 0.00001)				
5 Week 24/26, 20 mg e. week					
Van de Putte 2004	54/112	29/110	==	100.0 %	1.83 [1.27, 2.64]
Subtotal (95% CI)	112	110	•	100.0 %	1.83 [1.27, 2.64]
Total events: 54 (Treatment), 29 Heterogeneity: not applicable Test for overall effect: $Z = 3.23$ (6 Week 24/26, 20 mg e.o. week					
Van de Putte 2004	44/106	29/110	-	100.0 %	1.57 [1.07, 2.32]
Subtotal (95% CI)	106	110	•	100.0 %	1.57 [1.07, 2.32]
Total events: 44 (Treatment), 29 Heterogeneity: not applicable Test for overall effect: Z = 2.31 (7 Week 24/26, 40 mg e. week					
Van de Putte 2004	65/103	29/110	-	100.0 %	2.39 [1.69, 3.38]
Subtotal (95% CI)	103	110	•	100.0 %	2.39 [1.69, 3.38]
Total events: 65 (Treatment), 29 Heterogeneity: not applicable Test for overall effect: Z = 4.95 (8 Week 24/26, 40 mg e.o. week	(P < 0.00001)				
Van de Putte 2004	63/113	29/110	-	100.0 %	2.11 [1.49, 3.01]
Subtotal (95% CI) Total events: 63 (Treatment), 29 Heterogeneity: not applicable Test for overall effect: Z = 4.16 (110	•	100.0 %	2.11 [1.49, 3.01]

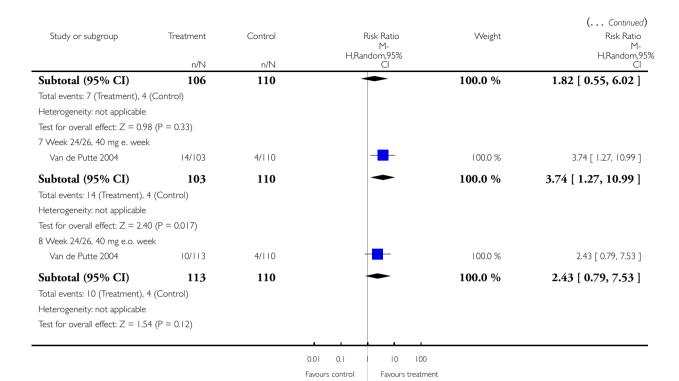
Favours control Favours treatment

Analysis 2.5. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 5 EULAR response: good.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 5 EULAR response: good

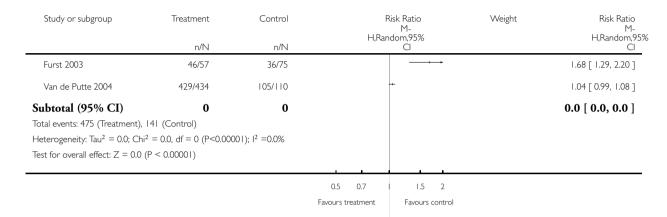




Analysis 2.6. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 6 Adverse events (all doses of adalimumab).

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 6 Adverse events (all doses of adalimumab)



Analysis 2.7. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 7 Serious adverse events (all doses of adalimumab).

Review: Adalimumab for treating rheumatoid arthritis

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 7 Serious adverse events (all doses of adalimumab)

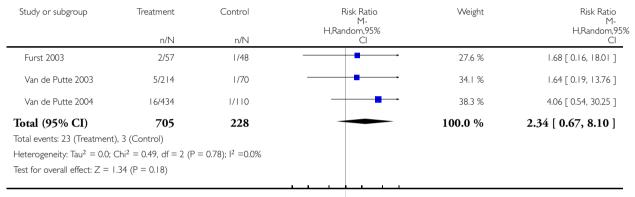
Study or subgroup	Treatment	Control	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl_
Furst 2003	3/57	2/48		6.0 %	1.26 [0.22, 7.25]
Van de Putte 2003	16/214	7/70		25.7 %	0.75 [0.32, 1.74]
Van de Putte 2004	53/434	16/110	-	68.3 %	0.84 [0.50, 1.41]
Total (95% CI)	705	228	•	100.0 %	0.84 [0.54, 1.28]
Total events: 72 (Treatmen	t), 25 (Control)				
Heterogeneity: Tau ² = 0.0;	$Chi^2 = 0.28$, $df = 2$ (P	= 0.87); I ² =0.0%			
Test for overall effect: Z =	0.82 (P = 0.41)				
			0.1 0.2 0.5 2 5 10		
			Favours treatment Favours control		

Analysis 2.8. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 8 Withdrawals due to adverse events (all doses of adalimumab).

Review: Adalimumab for treating rheumatoid arthritis

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 8 Withdrawals due to adverse events (all doses of adalimumab)

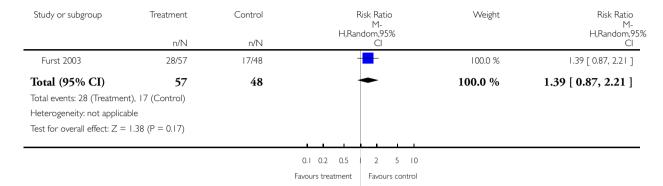


0.1 0.2 0.5 2 5 10 Favours treatment Favours control

Analysis 2.9. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 9 Infections.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 9 Infections

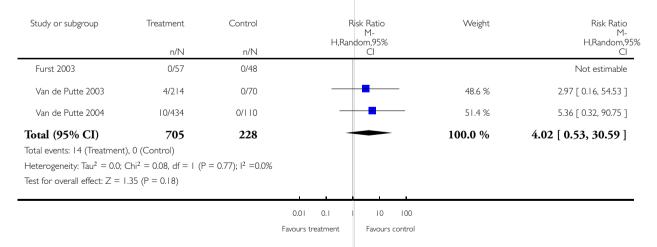


Analysis 2.10. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 10 Serious infections (all doses of adalimumab).

Review: Adalimumab for treating rheumatoid arthritis

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 10 Serious infections (all doses of adalimumab)

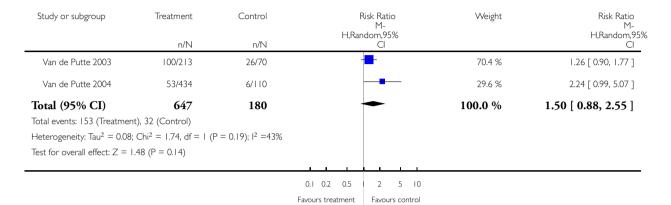


Analysis 2.11. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 11 ANA (all doses of adalimumab).

Review: Adalimumab for treating rheumatoid arthritis

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: II ANA (all doses of adalimumab)

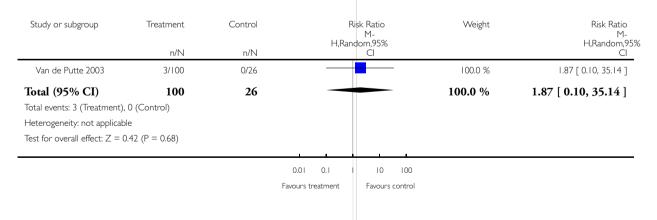


Analysis 2.12. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 12 AntiDNA.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

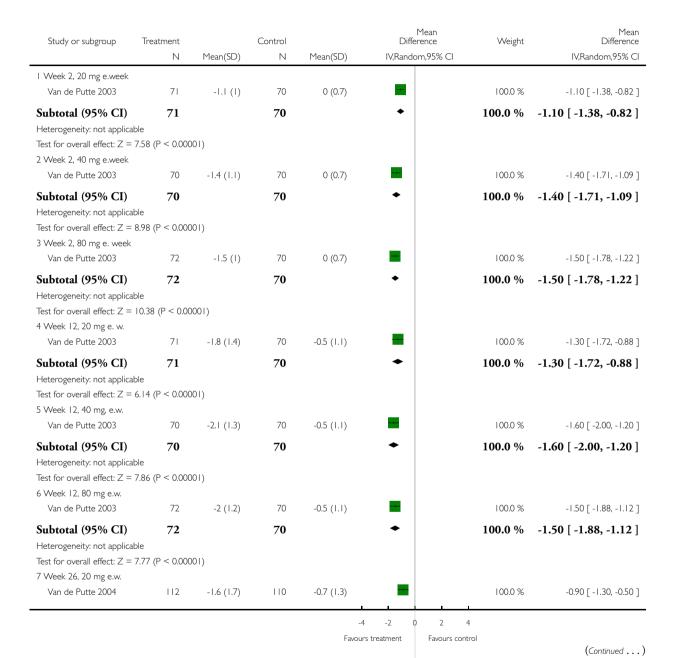
Outcome: 12 AntiDNA



Analysis 2.13. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 13 DAS28.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 13 DAS28



,	Continued)
 	(ontinuea)

Study or subgroup	Treatment		Control		Mean Difference	Weight	Mean Difference
,	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Subtotal (95% CI)	112		110		*	100.0 %	-0.90 [-1.30, -0.50]
Heterogeneity: not applical	ble						
Test for overall effect: $Z =$	4.44 (P < 0.000	01)					
8 Week 26, 20 mg e.o. we	ek						
Van de Putte 2004	106	-1.3 (1.6)	110	-0.7 (1.3)	-	100.0 %	-0.60 [-0.99, -0.21]
Subtotal (95% CI)	106		110		•	100.0 %	-0.60 [-0.99, -0.21]
Heterogeneity: not applical	ble						
Test for overall effect: $Z =$	3.02 (P = 0.002	5)					
9 Week 26, 40 mg e. week	<						
Van de Putte 2004	103	-2 (1.6)	110	-0.7 (1.3)	-	100.0 %	-1.30 [-1.69, -0.91]
Subtotal (95% CI) Heterogeneity: not applical	103		110		•	100.0 %	-1.30 [-1.69, -0.91]
Test for overall effect: $Z =$		01)					
	`	,					
10 Week 26, 40 mg e.o. w Van de Putte 2004	еек 113	-1.7 (1.6)	110	-0.7 (1.3)	=	100.0 %	-1.00 [-1.38, -0.62]
Subtotal (95% CI)	113	. ,	110	,	•	100.0 %	-1.00 [-1.38, -0.62]
Heterogeneity: not applical			110		•	100.0 70	-1.00 [-1.36, -0.02]
0 / 11		01)					
Test for overall effect: $Z =$	5.13 (P < 0.000	01)					
						i	

Favours treatment Favours control

Analysis 2.14. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 14 Tender joints.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 14 Tender joints



Favours treatment Favours control

		Continued)

Study or subgroup	Treatment		Control		Mean Difference	Weight	Mean Difference
,	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Subtotal (95% CI)	112		110		•	100.0 %	-8.30 [-12.55, -4.05]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	3.83 (P = 0.00	0013)					
8 Week 26, 20 mg e.o. we	ek						
Van de Putte 2004	106	-11.2 (14.9)	110	-6.6 (16.6)	•	100.0 %	-4.60 [-8.80, -0.40]
Subtotal (95% CI)	106		110		•	100.0 %	-4.60 [-8.80, -0.40]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	2.14 (P = 0.03	32)					
9 Week 26, 40 mg e. week	<						
Van de Putte 2004	103	-17.1 (15.5)	110	-6.6 (16.6)	•	100.0 %	-10.50 [-14.81, -6.19]
Subtotal (95% CI) Heterogeneity: not applica	103 ble		110		•	100.0 %	-10.50 [-14.81, -6.19]
Test for overall effect: $Z =$	4.77 (P < 0.00	0001)					
10 Week 26, 40 mg e.o. w	eek						
Van de Putte 2004	113	-13.6 (18.7)	110	-6.6 (16.6)	=	100.0 %	-7.00 [-11.64, -2.36]
Subtotal (95% CI)	113		110		•	100.0 %	-7.00 [-11.64, -2.36]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	2.96 (P = 0.00	031)					
						1	

Analysis 2.15. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 15 Swollen joints.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 15 Swollen joints

Study or subgroup 7	Freatment		Control		Mean Difference Weight		Mean Difference	
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI	
I Week 2, 20 mg e.week								
Van de Putte 2003	71	-4.6 (7.2)	70	-0.9 (5)	-	100.0 %	-3.70 [-5.74, -1.66]	
Subtotal (95% CI)	71		70		•	100.0 %	-3.70 [-5.74, -1.66]	
Heterogeneity: not applicable								
Test for overall effect: $Z = 3.5$	55 (P = 0.000	039)						
2 Week 2, 40 mg e.week					_			
Van de Putte 2003	70	-5 (6)	70	-0.9 (5)	-	100.0 %	-4.10 [-5.93, -2.27]	
Subtotal (95% CI)	70		70		•	100.0 %	-4.10 [-5.93, -2.27]	
Heterogeneity: not applicable								
Test for overall effect: $Z = 4.3$	39 (P = 0.000	0011)						
3 Week 2, 80 mg e. week					_			
Van de Putte 2003	72	-5.4 (7.6)	70	-0.9 (5)	-	100.0 %	-4.50 [-6.61, -2.39]	
Subtotal (95% CI)	72		70		•	100.0 %	-4.50 [-6.61, -2.39]	
Heterogeneity: not applicable								
Test for overall effect: $Z = 4.1$	18 (P = 0.000)	0029)						
4 Week 12, 20 mg e. w.					_			
Van de Putte 2003	71	-8.1 (8.2)	70	-2.8 (7.3)	-	100.0 %	-5.30 [-7.86, -2.74]	
Subtotal (95% CI)	71		70		•	100.0 %	-5.30 [-7.86, -2.74]	
Heterogeneity: not applicable								
Test for overall effect: $Z = 4.0$	05 (P = 0.000)	0050)						
5 Week 12, 40 mg, e.w.					_			
Van de Putte 2003	70	-9.6 (7.1)	70	-2.8 (7.3)	-	100.0 %	-6.80 [-9.19, -4.41]	
Subtotal (95% CI)	70		70		•	100.0 %	-6.80 [-9.19, -4.41]	
Heterogeneity: not applicable								
Test for overall effect: $Z = 5.5$	59 (P < 0.000	001)						
6 Week 12, 80 mg e.w.								
Van de Putte 2003	72	-10.7 (7.5)	70	-2.8 (7.3)		100.0 %	-7.90 [-10.33, -5.47	
Subtotal (95% CI)	72		70	-	•	100.0 %	-7.90 [-10.33, -5.47]	
Heterogeneity: not applicable								
Test for overall effect: $Z = 6.3$	36 (P < 0.000	001)						
7 Week 26, 20 mg e.w.								

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Study or subgroup	Treatment		Control		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Subtotal (95% CI)	112		110		-	100.0 %	-4.80 [-7.50, -2.10]
Heterogeneity: not applicat	ole						
Test for overall effect: $Z = 3$	3.48 (P = 0.000	050)					
8 Week 26, 20 mg e.o. wee	ek						
Van de Putte 2004	106	-5.7 (10.5)	110	-2.4 (9.5)	-	100.0 %	-3.30 [-5.97, -0.63]
Subtotal (95% CI)	106		110		-	100.0 %	-3.30 [-5.97, -0.63]
Heterogeneity: not applicab	ole						
Test for overall effect: $Z = 2$	2.42 (P = 0.01e	5)					
9 Week 26, 40 mg e. week							
Van de Putte 2004	103	-8.3 (10.8)	110	-2.4 (9.5)	-	100.0 %	-5.90 [-8.64, -3.16]
Subtotal (95% CI)	103		110		•	100.0 %	-5.90 [-8.64, -3.16]
Heterogeneity: not applicab	ole						
Test for overall effect: $Z = 4$	4.22 (P = 0.000	0024)					
10 Week 26, 40 mg e.o. we	eek						
Van de Putte 2004	113	-8.5 (10.6)	110	-2.4 (9.5)	-	100.0 %	-6.10 [-8.74, -3.46]
Subtotal (95% CI)	113		110		•	100.0 %	-6.10 [-8.74, -3.46]
Heterogeneity: not applicab	ole						
Test for overall effect: Z = 4	4.53 (P < 0.000	001)					

Analysis 2.16. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 16 Patient pain assessment.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 16 Patient pain assessment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV.Random,95% CI	Weight	Mean Difference IV,Random,95% CI
I Week 2, 20 mg e.week		(. ,		(- /			, ,
Van de Putte 2003	71	-25.8 (26.4)	70	-1.7 (22.3)	=	100.0 %	-24.10 [-32.16, -16.04]
Subtotal (95% CI)	71		70		•	100.0 %	-24.10 [-32.16, -16.04]
Heterogeneity: not applical	ole						
Test for overall effect: $Z =$	5.86 (P < 0.0	0001)					
2 Week 2, 40 mg e.week					_		
Van de Putte 2003	70	-26 (25.3)	70	-1.7 (22.3)	-	100.0 %	-24.30 [-32.20, -16.40]
Subtotal (95% CI)	70		70		•	100.0 %	-24.30 [-32.20, -16.40]
Heterogeneity: not applical	ole						
Test for overall effect: $Z =$	6.03 (P < 0.0	0001)					
3 Week 2, 80 mg e. week	70	2 (2 (20 0)	70	17 (22.2)		100000	24505 2140 1740 1
Van de Putte 2003	72	-26.2 (20.8)	70	-1.7 (22.3)	-	100.0 %	-24.50 [-31.60, -17.40]
Subtotal (95% CI)	72		70		•	100.0 %	-24.50 [-31.60, -17.40]
Heterogeneity: not applical							
Test for overall effect: $Z =$	6.77 (P < 0.0	0001)					
4 Week 12, 20 mg e. w.	71	210 (207)	70	70 (2(0)		100000	2400 5 22 10 1402 7
Van de Putte 2003	71	-31.8 (28.7)	70	-7.8 (26.9)	-	100.0 %	-24.00 [-33.18, -14.82]
Subtotal (95% CI)	71		70		•	100.0 %	-24.00 [-33.18, -14.82]
Heterogeneity: not applical							
Test for overall effect: $Z =$	5.12 (P < 0.0	0001)					
5 Week 12, 40 mg, e.w. Van de Putte 2003	70	25.2 (20.4)	70	70 (240)	_	100.0 %	-27.50 [-36.84, -18.16]
		-35.3 (29.4)		-7.8 (26.9)	-		
Subtotal (95% CI)	70		70		•	100.0 %	-27.50 [-36.84, -18.16]
Heterogeneity: not applical							
Test for overall effect: $Z =$	5.77 (P < 0.00	0001)					
6 Week 12, 80 mg e.w. Van de Putte 2003	72	20 1 (22 1)	70	70 (2/0)	_	100.0 %	-22.30 [-30.41, -14.19]
van de Putte 2003		-30.1 (22.1)		-7.8 (26.9)	-	100.0 %	
Subtotal (95% CI)	72		70		•	100.0 %	-22.30 [-30.41, -14.19]
Heterogeneity: not applical							
Test for overall effect: $Z = 7$	5.39 (P < 0.0)	0001)					
7 Week 26, 20 mg e.w.	112	25.2 (20.0)	110	11 (27.7)	_	100000	1430 5 3170 7737
Van de Putte 2004	112	-25.2 (30.8)	110	-11 (26.7)	•	100.0 %	-14.20 [-21.78, -6.62]
				-10	0 -50 0 50 1	00	
					s treatment Favours con		
							(5

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Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI)	112	r icari(3D)	110	r icari(5D)	◆	100.0 %	-14.20 [-21.78, -6.62]
Heterogeneity: not applica						10000 70	11.20 [211, 6, 6102]
Test for overall effect: Z =		0024)					
8 Week 26, 20 mg e.o. w	eek	,					
Van de Putte 2004	106	-20.1 (30.3)	110	-11 (26.7)	-	100.0 %	-9.10 [-16.73, -1.47]
Subtotal (95% CI)	106		110		•	100.0 %	-9.10 [-16.73, -1.47]
Heterogeneity: not applica	able						
Test for overall effect: Z =	= 2.34 (P = 0.0	19)					
9 Week 26, 40 mg e. wee	ek						
Van de Putte 2004	103	-32 (31.3)	110	-11 (26.7)	-	100.0 %	-21.00 [-28.84, -13.16]
Subtotal (95% CI)	103		110		•	100.0 %	-21.00 [-28.84, -13.16]
Heterogeneity: not applica	able						
Test for overall effect: Z =	= 5.25 (P < 0.00	0001)					
10 Week 26, 40 mg e.o. v	week						
Van de Putte 2004	113	-27.6 (31.1)	110	-11 (26.7)	-	100.0 %	-16.60 [-24.20, -9.00]
Subtotal (95% CI)	113		110		•	100.0 %	-16.60 [-24.20, -9.00]
Heterogeneity: not applica	able						
Test for overall effect: Z =	= 4.28 (P = 0.00	00019)					

Analysis 2.17. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 17 Patient global assessment.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 17 Patient global assessment

Week 2, 20 mg e-week	Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI) 71 70	I Week 2, 20 mg e.week							<u> </u>
Heterogeneity: not applicable Test for overall effect: Z = 5.48 (P < 0.00001) 2 Veek 2, 40 mg e. week Van de Putte 2003 70 -26.6 (29.6) 70 -1.3 (20.5) Subtotal (95% CI) 70 70 ↑ 100.0 % -25.30 [-33.73, -16.87] Heterogeneity: not applicable Test for overall effect: Z = 5.88 (P < 0.00001) 3 Veek 2, 80 mg e. week Van de Putte 2003 72 -26.8 (22.2) 70 -1.3 (20.5) ↑ 100.0 % -25.50 [-32.53, -18.47] Heterogeneity: not applicable Test for overall effect: Z = 7.11 (P < 0.00001) 4 Veek 12, 20 mg e. w Van de Putte 2003 71 -31.7 (28) 70 -6.9 (26) ↑ 100.0 % -24.80 [-33.72, -15.88] Subtotal (95% CI) 71 70 ↑ 100.0 % -24.80 [-33.72, -15.88] Heterogeneity: not applicable Test for overall effect: Z = 5.45 (P < 0.00001) 5 Veek 12, 40 mg e. w Van de Putte 2003 70 -37.6 (27.9) 70 -6.9 (26) ↑ 100.0 % -30.70 [-39.63, -21.77] Heterogeneity: not applicable Test for overall effect: Z = 5.47 (P < 0.00001) 5 Veek 12, 80 mg e.w. Van de Putte 2003 72 -31 (23.7) 70 -6.9 (26) ↑ 100.0 % -24.10 [-32.29, -15.91] Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) 70 -6.9 (26) ↑ 100.0 % -24.10 [-32.29, -15.91] Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) 70 -6.9 (26) ↑ 100.0 % -24.10 [-32.29, -15.91] Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) 70 -6.9 (26) ↑ 100.0 % -24.10 [-32.29, -15.91] Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) 70 -6.9 (26) ↑ 100.0 % -24.10 [-32.29, -15.91] Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) 70 -6.9 (26) ↑ 100.0 % -24.10 [-32.29, -15.91]	Van de Putte 2003	71	-24.2 (25.9)	70	-1.3 (20.5)	-	100.0 %	-22.90 [-30.60, -15.20]
Test for overall effect: Z = 5.83 (P < 0.00001) 2 Week 2, 40 mg eweek Van de Putte 2003 70 -26.6 (29.6) 70 -1.3 (20.5) ■ Subtotal (95% CI) 70 70 ↑ 100.0 % -25.30 [-33.73, -16.87] Heterogeneity, not applicable Test for overall effect: Z = 5.88 (P < 0.00001) 3 Week 2, 80 mg e. week Van de Putte 2003 72 -26.8 (22.2) 70 -1.3 (20.5) ■ Subtotal (95% CI) 72 70 ↑ 100.0 % -25.50 [-32.53, -18.47] Heterogeneity, not applicable Test for overall effect: Z = 7.11 (P < 0.00001) 4 Week 12, 20 mg e. w Van de Putte 2003 71 -31.7 (28) 70 -6.9 (26) ■ Subtotal (95% CI) 71 70 ↑ 100.0 % -24.80 [-33.72, -15.88] Heterogeneity, not applicable Test for overall effect: Z = 5.45 (P < 0.00001) 5 Week 12, 40 mg, e.w. Van de Putte 2003 70 -37.6 (27.9) 70 -6.9 (26) ■ Subtotal (95% CI) 70 ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -70 ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -70 ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -31 (23.7) ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -31 (23.7) ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -31 (23.7) ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -31 (23.7) ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -31 (23.7) ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -31 (23.7) ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -31 (23.7) ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -31 (23.7) ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -31 (23.7) ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -31 (23.7) ↑ -31 (23.7) ↑ -6.9 (26) ■ Subtotal (95% CI) 72 ↑ -31 (23.7)	Subtotal (95% CI)	71		70		•	100.0 %	-22.90 [-30.60, -15.20]
2 Week 2, 40 mg e.week	Heterogeneity: not applical	ble						
Subtotal (95% CI) 70 70 70 100.0 % -25.30 [-33.73, -16.87] Heterogeneity, not applicable Test for overall effect: Z = 5.88 (P < 0.00001) 3 Week 2, 80 mg e. week Van de Putte 2003 72 -26.8 (22.2) 70 -1.3 (20.5) 100.0 % -25.50 [-32.53, -18.47] Subtotal (95% CI) 72 70 100.0 % -25.50 [-32.53, -18.47] Heterogeneity, not applicable Test for overall effect: Z = 7.11 (P < 0.00001) 4 Week 12, 20 mg e. w. Van de Putte 2003 71 -31.7 (28) 70 -6.9 (26) 100.0 % -24.80 [-33.72, -15.88] Subtotal (95% CI) 71 70 100.0 % -24.80 [-33.72, -15.88] Subtotal (95% CI) 71 70 100.0 % -24.80 [-33.72, -15.88] Heterogeneity, not applicable Test for overall effect: Z = 5.45 (P < 0.00001) 5 Week 12, 40 mg e.w. Van de Putte 2003 70 -37.6 (27.9) 70 -6.9 (26) 100.0 % -30.70 [-39.63, -21.77] Heterogeneity, not applicable Test for overall effect: Z = 6.74 (P < 0.00001) 6 Week 12, 80 mg e.w. Van de Putte 2003 72 -31 (23.7) 70 -6.9 (26) 100.0 % -24.10 [-32.29, -15.91] Subtotal (95% CI) 72 70 -6.9 (26) 100.0 % -24.10 [-32.29, -15.91] Find the Putte 2003 72 -31 (23.7) 70 -6.9 (26) 100.0 % -24.10 [-32.29, -15.91] Find the Putte 2003 72 -31 (23.7) 70 -6.9 (26) 100.0 % -24.10 [-32.29, -15.91] Subtotal (95% CI) 72 70 -6.9 (26) 100.0 % -24.10 [-32.29, -15.91] Find the Putte 2003 72 -31 (23.7) 70 -6.9 (26) 100.0 % -24.10 [-32.29, -15.91] Find the Putte 2003 72 -31 (23.7) 70 -6.9 (26) 100.0 % -24.10 [-32.29, -15.91]		5.83 (P < 0.00	0001)					
Subtotal (95% CI) 70 70 ↑ 100.0 % -25.30 [-33.73, -16.87] Heterogeneity: not applicable Test for overall effect: Z = 5.88 (P < 0.00001) 3 Week 2, 80 mg e, week Van de Putte 2003 72 -26.8 (22.2) 70 -1.3 (20.5) The tetrogeneity: not applicable Test for overall effect: Z = 7.11 (P < 0.00001) 4 Week 12, 20 mg e, w. Van de Putte 2003 71 -31.7 (28) 70 -6.9 (26) Subtotal (95% CI) 71 70 Test for overall effect: Z = 5.45 (P < 0.00001) 5 Week 12, 20 mg e, w. Van de Putte 2003 70 -37.6 (27.9) 70 -6.9 (26) Subtotal (95% CI) 70 The tetrogeneity: not applicable Test for overall effect: Z = 5.47 (P < 0.00001) 5 Week 12, 40 mg e.w. Van de Putte 2003 70 -37.6 (27.9) 70 -6.9 (26) To overall effect: Z = 6.74 (P < 0.00001) Subtotal (95% CI) 70 The tetrogeneity: not applicable Test for overall effect: Z = 6.74 (P < 0.00001) Subtotal (95% CI) 70 The tetrogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) Test for overall effect: Z = 5.77 (P < 0.00001) Test for overall effect: Z = 5.77 (P < 0.00001) The tetrogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) The tetrogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) To overall effect: Z = 5.77 (P < 0.00001) To overall effect: Z = 5.77 (P < 0.00001) To overall effect: Z = 5.77 (P < 0.00001) To overall effect: Z = 5.77 (P < 0.00001)	-	70	2///20/)	70	1.2 (20.5)	_	100000/	25 20 [22 72]/ 07]
Heterogeneity: not applicable Test for overall effect: Z = 5.88 (P < 0.00001) 3 Week 2, 80 mg e. week Van de Putte 2003 72 -26.8 (222) 70 -1.3 (205) ■ 100.0 % -25.50 [-32.53, -18.47] Heterogeneity: not applicable Test for overall effect: Z = 7.11 (P < 0.00001) 4 Week 12, 20 mg e. w Van de Putte 2003 71 -31.7 (28) 70 -6.9 (26) ■ 100.0 % -24.80 [-33.72, -15.88] Heterogeneity: not applicable Test for overall effect: Z = 5.45 (P < 0.00001) 5 Week 12, 40 mg e.w. Van de Putte 2003 70 -37.6 (27.9) 70 -6.9 (26) ■ 100.0 % -30.70 [-39.63, -21.77] Subtotal (95% CI) 70			-26.6 (29.6)		-1.3 (20.5)	-		
Test for overall effect: Z = 5.88 (P < 0.00001) 3 Week 2, 80 mg e. week Van de Putte 2003 72 -26.8 (22.2) 70 -1.3 (20.5) 100.0 % -25.50 [-32.53, -18.47] Heterogeneity: not applicable Test for overall effect: Z = 7.11 (P < 0.00001) 4 Week 12, 20 mg e. w. Van de Putte 2003 71 -31.7 (28) 70 -6.9 (26) 100.0 % -24.80 [-33.72, -15.88] Subtotal (95% CI) 71 70		, -		70		•	100.0 %	-25.30 [-33.73, -16.87]
3 Week 2, 80 mg e. week			2001)					
Van de Putte 2003 72 -2.68 (22.2) 70 -1.3 (20.5)		5.88 (P < 0.00	5001)					
Heterogeneity: not applicable Test for overall effect: Z = 7.11 (P < 0.00001) 4 Week 12, 20 mg e. w. Van de Putte 2003 71 -31.7 (28) 70 -6.9 (26) Bubtotal (95% CI) 71 70	-	72	-26.8 (22.2)	70	-1.3 (20.5)		100.0 %	-25.50 [-32.53, -18.47]
Heterogeneity: not applicable Test for overall effect: Z = 7.11 (P < 0.00001) 4 Week 12, 20 mg e. w. Van de Putte 2003 71 -31.7 (28) 70 -6.9 (26) ■ 100.0 % -24.80 [-33.72, -15.88] Subtotal (95% CI) 71 70 Heterogeneity: not applicable Test for overall effect: Z = 5.45 (P < 0.00001) 5 Week 12, 40 mg e.w. Van de Putte 2003 70 -37.6 (27.9) 70 70 ■ 100.0 % -30.70 [-39.63, -21.77] Subtotal (95% CI) 70 70 Heterogeneity: not applicable Test for overall effect: Z = 6.74 (P < 0.00001) 6 Week 12, 80 mg e.w. Van de Putte 2003 72 -31 (23.7) 70 -6.9 (26) ■ 100.0 % -30.70 [-39.63, -21.77] Subtotal (95% CI) 72 70 ■ 100.0 % -24.10 [-32.29, -15.91] Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) 7 Week 26, 20 mg e.w. Van de Putte 2004 112 -26.5 (31.6) 110 -10.6 (27.8) ■ 100.0 % -24.10 [-32.29, -15.91]	Subtotal (05% CI)	72		70		•	100 0 %	25 50 [32 53 .18 /7]
4 Week 12, 20 mg e. w. Van de Putte 2003 71 -31.7 (28) 70 -6.9 (26) ■ 100.0 % -24.80 [-33.72, -15.88 Subtotal (95% CI) 71 70 ■ 100.0 % -24.80 [-33.72, -15.88 Heterogeneity: not applicable Test for overall effect: Z = 5.45 (P < 0.00001) 5 Week 12, 40 mg, e.w. Van de Putte 2003 70 -37.6 (27.9) 70 -6.9 (26) ■ 100.0 % -30.70 [-39.63, -21.77 Subtotal (95% CI) 70 70 ■ 100.0 % -30.70 [-39.63, -21.77 Heterogeneity: not applicable Test for overall effect: Z = 6.74 (P < 0.00001) 6 Week 12, 80 mg e.w. Van de Putte 2003 72 -31 (23.7) 70 -6.9 (26) ■ 100.0 % -24.10 [-32.29, -15.91 Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) 7 Week 26, 20 mg e.w. Van de Putte 2004 112 -26.5 (31.6) 110 -10.6 (27.8) ■ 100.0 % -15.90 [-23.73, -8.07		, –		70			100.0 /0	-23.30 [-32.33; -10. 1 /]
Van de Putte 2003 71 -31.7 (28) 70 -6.9 (26) ■ 100.0 % -24.80 [-33.72, -15.88 Subtotal (95% CI) 71 70 ◆ 100.0 % -24.80 [-33.72, -15.88 Heterogeneity: not applicable Test for overall effect: Z = 5.45 (P < 0.00001)		7.11 (P < 0.00	0001)					
Subtotal (95% CI) 71 70 ← 100.0 % -24.80 [-33.72, -15.88 Heterogeneity: not applicable Test for overall effect: Z = 5.45 (P < 0.00001) 5 Week 12, 40 mg, e.w. Van de Putte 2003 70 -37.6 (27.9) 70 -6.9 (26)	-	71	-317 (28)	70	-69 (26)	_	1000%	-24 80 [-33 72 -15 88]
Heterogeneity: not applicable Test for overall effect: Z = 5.45 (P < 0.00001) 5 Week 12, 40 mg, e.w. Van de Putte 2003 70 -37.6 (27.9) 70 -6.9 (26) Bubtotal (95% CI) 70			31.7 (20)		0.7 (20)	_		2
Test for overall effect: Z = 5.45 (P < 0.00001) 5 Week 12, 40 mg, e.w. Van de Putte 2003 70 -37.6 (27.9) 70 -6.9 (26) Subtotal (95% CI) 70 70 Heterogeneity: not applicable Test for overall effect: Z = 6.74 (P < 0.00001) 6 Week 12, 80 mg e.w. Van de Putte 2003 72 -31 (23.7) 70 -6.9 (26) Subtotal (95% CI) 72 70 Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) 7 Week 26, 20 mg e.w. Van de Putte 2004 112 -26.5 (31.6) 110 -10.6 (27.8) 100.0 % -30.70 [-39.63, -21.77 100.0 % -30.70 [-39.63, -21.77 100.0 % -24.10 [-32.29, -15.91 100.0 % -24.10 [-32.29, -15.91 100.0 % -24.10 [-32.29, -15.91 100.0 % -15.90 [-23.73, -8.07		•		70		•	100.0 %	-24.80 [-33.72, -15.88]
5 Week 12, 40 mg, e.w. Van de Putte 2003 70 -37.6 (27.9) 70 -6.9 (26) Subtotal (95% CI) 70 ↑ 100.0 % -30.70 [-39.63, -21.77 Heterogeneity: not applicable Test for overall effect: Z = 6.74 (P < 0.00001) 6 Week 12, 80 mg e.w. Van de Putte 2003 72 -31 (23.7) 70 -6.9 (26) Subtotal (95% CI) 72 70 ↑ 100.0 % -24.10 [-32.29, -15.91 Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) 7 Week 26, 20 mg e.w. Van de Putte 2004 112 -26.5 (31.6) 110 -10.6 (27.8) 100.0 % -30.70 [-39.63, -21.77 100.0 % -24.10 [-32.29, -15.91 100.0 % -24.10 [-32.29, -15.91 100.0 % -24.10 [-32.29, -15.91 100.0 % -24.10 [-32.29, -15.91 100.0 % -24.10 [-32.29, -15.91 100.0 % -24.10 [-32.29, -15.91 100.0 % -24.10 [-32.29, -15.91 100.0 % -24.10 [-32.29, -15.91 100.0 % -24.10 [-32.29, -15.91			0001)					
Subtotal (95% CI) 70		3. 13 (1 - 0.00	5001)					
Heterogeneity: not applicable Test for overall effect: Z = 6.74 (P < 0.00001) 6 Week 12, 80 mg e.w. Van de Putte 2003 72 -31 (23.7) 70 -6.9 (26) Subtotal (95% CI) 72 70 Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) 7 Week 26, 20 mg e.w. Van de Putte 2004 112 -26.5 (31.6) 110 -10.6 (27.8) 100.0 % -24.10 [-32.29, -15.91] 100.0 % -24.10 [-32.29, -15.91] 100.0 % -15.90 [-23.73, -8.07]	Van de Putte 2003	70	-37.6 (27.9)	70	-6.9 (26)	=	100.0 %	-30.70 [-39.63, -21.77]
Heterogeneity: not applicable Test for overall effect: Z = 6.74 (P < 0.00001) 6 Week 12, 80 mg e.w. Van de Putte 2003 72 -31 (23.7) 70 -6.9 (26) Subtotal (95% CI) 72 70 Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) 7 Week 26, 20 mg e.w. Van de Putte 2004 112 -26.5 (31.6) 110 -10.6 (27.8) 100.0 % -24.10 [-32.29, -15.91] 100.0 % -24.10 [-32.29, -15.91] 100.0 % -15.90 [-23.73, -8.07]	Subtotal (95% CI)	70		70		•	100.0 %	-30.70 [-39.63, -21.77]
6 Week 12, 80 mg e.w. Van de Putte 2003 72 -31 (23.7) 70 -6.9 (26) Subtotal (95% CI) 72 70 Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) 7 Week 26, 20 mg e.w. Van de Putte 2004 112 -26.5 (31.6) 110 -10.6 (27.8) 100.0 % -24.10 [-32.29, -15.91] 100.0 % -24.10 [-32.29, -15.91] 100.0 % -15.90 [-23.73, -8.07]	Heterogeneity: not applical	ble						
Van de Putte 2003 72 -31 (23.7) 70 -6.9 (26) ■ 100.0 % -24.10 [-32.29, -15.91 Subtotal (95% CI) 72 70 ◆ 100.0 % -24.10 [-32.29, -15.91 Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001)	Test for overall effect: $Z =$	6.74 (P < 0.00	0001)					
Subtotal (95% CI) 72 70	G					_		
Heterogeneity: not applicable Test for overall effect: Z = 5.77 (P < 0.00001) 7 Week 26, 20 mg e.w. Van de Putte 2004 112 -26.5 (31.6) 110 -10.6 (27.8) 100.0 % -15.90 [-23.73, -8.07	Van de Putte 2003	72	-31 (23.7)	70	-6.9 (26)	-	100.0 %	-24.10 [-32.29, -15.91]
Test for overall effect: Z = 5.77 (P < 0.00001) 7 Week 26, 20 mg e.w. Van de Putte 2004	Subtotal (95% CI)	72		70		•	100.0 %	-24.10 [-32.29, -15.91]
7 Week 26, 20 mg e.w. Van de Putte 2004 112 -26.5 (31.6) 110 -10.6 (27.8) 100.0 % -15.90 [-23.73, -8.07]	- ,							
Van de Putte 2004 112 -26.5 (31.6) 110 -10.6 (27.8) 100.0 % -15.90 [-23.73, -8.07		5.77 (P < 0.00	0001)					
-100 -50 0 50 100	-	112	265 (217)	110	10 4 (27 9)	_	1000 %	15.90 [22.72 0.07.1
	van de Putte 2004	112	-26.3 (31.6)	110	-10.6 (27.8)		100.0 %	-13.90 [-23.73, -8.07]
Favours treatment Favours control					-10	0 -50 0 50 I	00	
Tayours a caution.					Favour	rs treatment Favours con	trol	

Adalimumab for treating rheumatoid arthritis (Review)
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		Continued)

Ν		Control		Difference	Weight	Mean Difference	
1.4	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI	
112		110		+	100.0 %	-15.90 [-23.73, -8.07]	
P = 0.00	00068)						
106	-19.5 (29.9)	110	-10.6 (27.8)	-	100.0 %	-8.90 [-16.61, -1.19]	
106		110		•	100.0 %	-8.90 [-16.61, -1.19]	
P = 0.02	24)						
103	-35 (31.5)	110	-10.6 (27.8)	-	100.0 %	-24.40 [-32.40, -16.40]	
103		110		•	100.0 %	-24.40 [-32.40, -16.40]	
P < 0.00	0001)						
113	-27.9 (30.5)	110	-10.6 (27.8)	-	100.0 %	-17.30 [-24.96, -9.64]	
113		110		•	100.0 %	-17.30 [-24.96, -9.64]	
(P < 0.00	0001)						
	106 106 106 103 103 103 113	(P = 0.000068) 106 -19.5 (29.9) 106 (P = 0.024) 103 -35 (31.5) 103 4 (P < 0.00001)	106 -19.5 (29.9) 110 106 110 106 110 107 107 110 108 110 109 (P = 0.024) 109 -35 (31.5) 110 109 (P < 0.00001) 110 111 110	106 -19.5 (29.9)	106 -19.5 (29.9) 110 -10.6 (27.8) 106 110 (P = 0.024) 103 -35 (31.5) 110 -10.6 (27.8) 103 110 (P < 0.00001) 113 -27.9 (30.5) 110 -10.6 (27.8)	106 -19.5 (29.9) 110 -10.6 (27.8) 100.0 % 106 110 100.0 % 107 -10.6 (27.8) 100.0 % 108 -35 (31.5) 110 -10.6 (27.8) 100.0 % 109 (P < 0.00001) 113 -27.9 (30.5) 110 -10.6 (27.8) 100.0 % 113 110 110 100.0 %	

Analysis 2.18. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 18 Physician global assessment.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 18 Physician global assessment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV.Random,95% CI	Weight	Mean Difference IV.Random,95% CI
114/ 12/20		T Ican(SD)	- 11	r ican(5D)	14,141140111,7576 CI		14,1 tai 100111,7370 Ci
I Week 2, 20 mg e.week Van de Putte 2003	71	-19.6 (18.9)	70	-2.3 (18.4)	-	100.0 %	-17.30 [-23.46, -11.14]
Subtotal (95% CI)	71		70		•	100.0 %	-17.30 [-23.46, -11.14]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	5.51 (P < 0.0	0001)					
2 Week 2, 40 mg e.week							
Van de Putte 2003	70	-20.7 (22.8)	70	-2.3 (18.4)	-	100.0 %	-18.40 [-25.26, -11.54]
Subtotal (95% CI)	70		70		•	100.0 %	-18.40 [-25.26, -11.54]
Heterogeneity: not applica	ble						
Test for overall effect: Z =	5.25 (P < 0.0	0001)					
3 Week 2, 80 mg e. week					_		
Van de Putte 2003	72	-24.3 (20.4)	70	-2.3 (18.4)	-	100.0 %	-22.00 [-28.39, -15.61]
Subtotal (95% CI)	72		70		•	100.0 %	-22.00 [-28.39, -15.61]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	6.75 (P < 0.0	0001)					
4 Week 12, 20 mg e. w.					_		
Van de Putte 2003	71	-28.8 (23.3)	70	-5 (22)	-	100.0 %	-23.80 [-31.28, -16.32]
Subtotal (95% CI)	71		70		•	100.0 %	-23.80 [-31.28, -16.32]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	6.24 (P < 0.0	0001)					
5 Week 12, 40 mg, e.w.					_		
Van de Putte 2003	70	-35.7 (20.3)	70	-5 (22)	-	100.0 %	-30.70 [-37.71, -23.69]
Subtotal (95% CI)	70		70		•	100.0 %	-30.70 [-37.71, -23.69]
Heterogeneity: not applica	ble						
Test for overall effect: Z =	8.58 (P < 0.0	0001)					
6 Week 12, 80 mg e.w.							
Van de Putte 2003	72	-33.4 (21.1)	70	-5 (22)		100.0 %	-28.40 [-35.49, -21.31]
Subtotal (95% CI)	72		70		•	100.0 %	-28.40 [-35.49, -21.31]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	7.85 (P < 0.0	0001)					
7 Week 26, 20 mg e.w.							
Van de Putte 2004	112	-26.4 (28.8)	110	-10.9 (25.4)		100.0 %	-15.50 [-22.64, -8.36]
					00 -50 0 50	100	
					urs treatment Favours		
				. 2700	1.0413		(6 : 1)

Adalimumab for treating rheumatoid arthritis (Review)
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		Continued)	

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI)	112		110	. ,	•	100.0 %	-15.50 [-22.64, -8.36]
Heterogeneity: not application	able						
Test for overall effect: Z =	= 4.25 (P = 0.00	00021)					
8 Week 26, 20 mg e.o. w	eek						
Van de Putte 2004	106	-20.5 (27)	110	-10.9 (25.4)	-	100.0 %	-9.60 [-16.60, -2.60]
Subtotal (95% CI)	106		110		•	100.0 %	-9.60 [-16.60, -2.60]
Heterogeneity: not application	able						
Test for overall effect: Z =	= 2.69 (P = 0.00	072)					
9 Week 26, 40 mg e. wee	ek				_		
Van de Putte 2004	103	-32.5 (27.3)	110	-10.9 (25.4)	-	100.0 %	-21.60 [-28.69, -14.51]
Subtotal (95% CI)	103		110		•	100.0 %	-21.60 [-28.69, -14.51]
Heterogeneity: not applica	able						
Test for overall effect: Z =	= 5.97 (P < 0.00	0001)					
10 Week 26, 40 mg e.o. v	week						
Van de Putte 2004	113	-27.3 (28.8)	110	-10.9 (25.4)	-	100.0 %	-16.40 [-23.52, -9.28]
Subtotal (95% CI)	113		110		•	100.0 %	-16.40 [-23.52, -9.28]
Heterogeneity: not applica	able						
Test for overall effect: Z =	= 4.51 (P < 0.00	0001)					
						Î	

Analysis 2.19. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 19 HAQ.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 19 HAQ

Study or subgroup	Treatment		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
I Week 2, 20 mg e.week					_		
Van de Putte 2003	71	-0.34 (0.42)	70	0.05 (0.38)		100.0 %	-0.39 [-0.52, -0.26]
Subtotal (95% CI)	71		70		•	100.0 %	-0.39 [-0.52, -0.26]
Heterogeneity: not applicab	ole						
Test for overall effect: $Z = \frac{1}{2}$	5.78 (P < 0.00	001)					
2 Week 2, 40 mg e.week					_		
Van de Putte 2003	70	-0.28 (0.33)	70	0.05 (0.38)	=	100.0 %	-0.33 [-0.45, -0.21]
Subtotal (95% CI)	70		70		•	100.0 %	-0.33 [-0.45, -0.21]
Heterogeneity: not applicab	ole						
Test for overall effect: $Z = \frac{1}{2}$	5.49 (P < 0.00	001)					
3 Week 2, 80 mg e. week							
Van de Putte 2003	72	-0.3 (0.45)	70	0.05 (0.38)	-	100.0 %	-0.35 [-0.49, -0.21]
Subtotal (95% CI)	72		70		•	100.0 %	-0.35 [-0.49, -0.21]
Heterogeneity: not applicab	ole						
Test for overall effect: $Z = 5$	5.01 (P < 0.00	001)					
4 Week 12, 20 mg e. w.							
Van de Putte 2003	71	-0.45 (0.46)	70	-0.04 (0.37)	-	100.0 %	-0.41 [-0.55, -0.27]
Subtotal (95% CI)	71		70		•	100.0 %	-0.41 [-0.55, -0.27]
Heterogeneity: not applicab	ole						1 1 2 2 7 1 1 1
Test for overall effect: $Z = 5$	5.84 (P < 0.00	001)					
5 Week 12, 40 mg, e.w.							
Van de Putte 2003	70	-0.47 (0.43)	70	-0.04 (0.37)	-	100.0 %	-0.43 [-0.56, -0.30]
Subtotal (95% CI)	70		70		•	100.0 %	-0.43 [-0.56, -0.30]
Heterogeneity: not applicab	ole		, -				
Test for overall effect: $Z = 6$		001)					
6 Week 12, 80 mg e.w.	`	,					
Van de Putte 2003	72	-0.48 (0.5)	70	-0.04 (0.37)	-	100.0 %	-0.44 [-0.58, -0.30]
Subtotal (95% CI)	72		70		•	100.0 %	-0.44 [-0.58, -0.30]
Heterogeneity: not applicab	•						
Test for overall effect: $Z = 5$		001)					
7 Week 26, 20 mg e.w.	•	•					
Van de Putte 2004	112	-0.39 (0.62)	110	-0.07 (0.49)	-	100.0 %	-0.32 [-0.47, -0.17]
						i	
				=	I -0.5 0 0.5	I	

Favours treatment

(Continued . . .)

Favours control

(... Continued)

Treatment		Control		Mean Difference	Weight	Mean Difference	
Ν	Mean(SD)	Mean(SD) N Mear		IV,Random,95% CI		IV,Random,95% CI	
112		110		•	100.0 %	-0.32 [-0.47, -0.17]	
2							
27 (P = 0.00	0020)						
106	-0.29 (0.63)	110	-0.07 (0.49)	-	100.0 %	-0.22 [-0.37, -0.07]	
106		110		•	100.0 %	-0.22 [-0.37, -0.07]	
e							
86 (P = 0.00	43)						
103	-0.49 (0.54)	110	-0.07 (0.49)	-	100.0 %	-0.42 [-0.56, -0.28]	
103		110		•	100.0 %	-0.42 [-0.56, -0.28]	
2							
93 (P < 0.00	001)						
ek							
113	-0.38 (0.6)	110	-0.07 (0.49)	=	100.0 %	-0.31 [-0.45, -0.17]	
113		110		•	100.0 %	-0.31 [-0.45, -0.17]	
9							
23 (P = 0.00	0023)						
	N 112 27 (P = 0.000 106 106 103 103 103 103 113 113	N Mean(SD) 112 27 (P = 0.000020) 106 -0.29 (0.63) 106 886 (P = 0.0043) 103 -0.49 (0.54) 103 93 (P < 0.00001) 8k 113 -0.38 (0.6) 113	N Mean(SD) N 112 110 27 (P = 0.000020) 106 -0.29 (0.63) 110 106 110 286 (P = 0.0043) 103 -0.49 (0.54) 110 103 110 293 (P < 0.00001) 286 113 -0.38 (0.6) 110 113 110	N Mean(SD) N Mean(SD) 112 110 27 (P = 0.000020) 106 -0.29 (0.63) 110 -0.07 (0.49) 106 110 286 (P = 0.0043) 103 -0.49 (0.54) 110 -0.07 (0.49) 103 110 293 (P < 0.00001) 284 113 -0.38 (0.6) 110 -0.07 (0.49) 113	N Mean(SD) N Mean(SD) IV,Random,95% CI 112	N Mean(SD) N Mean(SD) IV,Random,95% CI 112	

-I -0.5 0 0.5 I
Favours treatment Favours control

Analysis 2.20. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 20 ESR.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 20 ESR

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
I Week 2, 20 mg e.week			70	0.5 (1.4.7)		10000	
Van de Putte 2003	71	-14.8 (20.8)	70	2.5 (16.7)	-	100.0 %	-17.30 [-23.52, -11.08]
Subtotal (95% CI) Heterogeneity: not applicab	71 le		70		•	100.0 %	-17.30 [-23.52, -11.08]
Test for overall effect: $Z = 5$	5.45 (P < 0.00	0001)					
2 Week 2, 40 mg e.week Van de Putte 2003	70	-14.3 (18.1)	70	2.5 (16.7)	-	100.0 %	-16.80 [-22.57, -11.03]
		()		215 (1017)			-
Subtotal (95% CI) Heterogeneity: not applicab	70		70		•	100.0 %	-16.80 [-22.57, -11.03]
Test for overall effect: $Z = 5$		0001)					
3 Week 2, 80 mg e.week	(. 5.5	3001)					
Van de Putte 2003	72	-15.7 (18.1)	70	2.5 (16.7)	-	100.0 %	-18.20 [-23.93, -12.47]
Subtotal (95% CI)	72		70		•	100.0 %	-18.20 [-23.93, -12.47]
Heterogeneity: not applicab	le						
Test for overall effect: $Z = 6$	5.23 (P < 0.00	0001)					
4 Week 12, 20 mg e. week							
Van de Putte 2003	71	-14.2 (21.8)	70	-2 (20.1)	-	100.0 %	-12.20 [-19.12, -5.28]
Subtotal (95% CI)	71		70		•	100.0 %	-12.20 [-19.12, -5.28]
Heterogeneity: not applicab							
Test for overall effect: $Z = 3$	3.46 (P = 0.00	0055)					
5 Week 12, 40 mg e. w. Van de Putte 2003	70	-17.9 (20)	70	-2 (20.1)	_	100.0 %	-15.90 [-22.54, -9.26]
		17.7 (20)		2 (20.1)			
Subtotal (95% CI)	70		70		•	100.0 %	-15.90 [-22.54, -9.26]
Heterogeneity: not applicab Test for overall effect: $Z = 4$		0001)					
6 Week 12, 80 mg, e.w.	1.07 (1 - 0.01	0001)					
Van de Putte 2003	72	-17.3 (20.6)	70	-2 (20.1)	-	100.0 %	-15.30 [-21.99, -8.61]
Subtotal (95% CI) Heterogeneity: not applicab			70		•	100.0 %	-15.30 [-21.99, -8.61]
Test for overall effect: $Z = 4$	H.48 (P < 0.00	0001)					

Favours treatment

Favours control

Adalimumab for treating rheumatoid arthritis (Review)
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Analysis 2.21. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 21 CRP.

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 21 CRP

Study or subgroup	Treatment		Control		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
I Week 2, 20 mg e.week							
Van de Putte 2003	71	-30 (41)	70	-2 (35)	-	100.0 %	-28.00 [-40.58, -15.42]
Subtotal (95% CI)	71		70		•	100.0 %	-28.00 [-40.58, -15.42]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	4.36 (P = 0.00	0013)					
2 Week 2, 40 mg e. week							
Van de Putte 2003	70	-29 (30)	70	-2 (35)	-	100.0 %	-27.00 [-37.80, -16.20]
Subtotal (95% CI)	70		70		•	100.0 %	-27.00 [-37.80, -16.20]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	4.90 (P < 0.00	001)					
3 Week 12, 80 mg e. w.					_		
Van de Putte 2003	72	-35 (44)	70	-2 (35)	-	100.0 %	-33.00 [-46.06, -19.94]
Subtotal (95% CI)	72		70		•	100.0 %	-33.00 [-46.06, -19.94]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	4.95 (P < 0.00	001)					
4 Week 12, 20 mg, e.w.							
Van de Putte 2003	71	-24 (3.1)	70	-1 (3.4)		100.0 %	-23.00 [-24.07, -21.93]
Subtotal (95% CI)	71		70		•	100.0 %	-23.00 [-24.07, -21.93]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	41.96 (P < 0.0	0001)					
5 Week 12, 40 mg e.w.							
Van de Putte 2003	70	-32 (3.4)	70	-1 (3.4)	•	100.0 %	-31.00 [-32.13, -29.87]
Subtotal (95% CI)	70		70		•	100.0 %	-31.00 [-32.13, -29.87]
Heterogeneity: not applica	ble						
Test for overall effect: $Z =$	53.94 (P < 0.0	0001)					
6 Week 26, 80 mg e.w.							
Van de Putte 2003	72	-34 (35)	70	-1 (3.4)	•	100.0 %	-33.00 [-41.12, -24.88]
Subtotal (95% CI)	72		70		•	100.0 %	-33.00 [-41.12, -24.88]
Heterogeneity: not applica	ble						
Test for overall effect: Z =	7.96 (P < 0.00	001)					

Favours treatment

50 100 Favours control

Analysis 2.22. Comparison 2 Adalimumab s.c. in monotherapy vs placebo, Outcome 22 Withdrawals.

Review: Adalimumab for treating rheumatoid arthritis

Comparison: 2 Adalimumab s.c. in monotherapy vs placebo

Outcome: 22 Withdrawals

Study or subgroup	Treatment n/N	Control n/N			Risk Ratio M- ndom,95% CI		Weight	Risk Ratio M- H,Random,95% Cl
Van de Putte 2003	28/214	23/70	_	-			18.0 %	0.40 [0.25, 0.64]
Van de Putte 2004	118/434	62/110		-			82.0 %	0.48 [0.39, 0.60]
Total (95% CI)	648	180		•			100.0 %	0.47 [0.38, 0.57]
Total events: 146 (Treatmer	nt), 85 (Control)							
Heterogeneity: Tau ² = 0.0;	$Chi^2 = 0.5 I, df = I (P$	= 0.47); I ² =0.0%						
Test for overall effect: $Z = \frac{1}{2}$	7.34 (P < 0.00001)							
			0.2	0.5	2	5		
			Favours t	reatment	Favours	control		

WHAT'S NEW

Last assessed as up-to-date: 19 May 2005.

Date	Event	Description
19 September 2008	Amended	Converted to new review format. C003-R

HISTORY

Protocol first published: Issue 1, 2005 Review first published: Issue 3, 2005

CONTRIBUTIONS OF AUTHORS

RAA: protocol, search strategy, quality assessment, data extraction, analysis, text of review

BHC: protocol, quality assessment, data extraction, analysis.

IVT: search strategy.

FNS: background, overview.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal [*therapeutic use]; Antibodies, Monoclonal, Humanized; Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Drug Therapy, Combination; Methotrexate [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans