Adalimumab for Treating Rheumatoid Arthritis

FEDERICO NAVARRO-SARABIA, RAFAEL ARIZA-ARIZA, BLANCA HERNÁNDEZ-CRUZ, and ISIDRO VILLANUEVA

ABSTRACT. ***Objective.*** To assess the efficacy and safety of adalimumab in the treatment of rheumatoid arthritis (RA).

Methods. A Cochrane systematic review was performed. The literature search, selection and assessment of the methodological quality of the studies, and the data extraction were performed according to the standard methodology of the Cochrane reviews. Outcome measures included American College of Rheumatology (ACR) and European League Against Rheumatism responses, Disease Activity Score 28 and components of the ACR response, and radiographic and safety data. Weighted mean difference and relative risk were used for reporting continuous and dichotomous data, respectively. Number needed to treat (NNT) or to harm (NNH) were estimated when appropriate. When significant heterogeneity was not found, data were pooled.

Results. Six studies with 2390 patients were included in this review. With adalimumab 40 mg every other week (eow) + methotrexate versus placebo + methotrexate, the absolute risk differences to achieve an ACR20, ACR50, and ACR70 response at 52 weeks were 35%, 32%, and 19% with NNT of 2.9, 3.1, and 5.3, respectively. At 52 weeks, adalimumab 40 mg eow and 20 mg every week (ew) significantly slowed the radiological progression. With adalimumab 40 mg eow versus placebo, the absolute risk differences to achieve an ACR20, ACR50, and ACR70 response at 24/26 weeks were 23.64%, 15.31%, and 12.22% with NNT of 5.0, 7.0, and 9.0, respectively. In most of the analyzed studies and comparisons, there were no significant differences in safety outcomes between adalimumab and control groups.

Conclusion. On the basis of studies reviewed here, adalimumab is efficacious in the treatment of RA. No serious adverse effects occurred. (First Release May 1, 2006; J Rheumatol 2006;33:1075–81)

Key Indexing Terms:
ADALIMUMAB RHEUMATOID ARTHRITIS COCHRANE SYSTEMATIC REVIEW

Rheumatoid arthritis (RA) is a systemic inflammatory disease associated with significant morbidity, disability, and impaired quality of life. Disease modifying antirheumatic drugs (DMARD) have been shown to be efficacious in treatment of RA. However, most patients experience only partial benefit taking traditional DMARD, and many are unable to tolerate these agents for long periods.

It has been found that tumor necrosis factor-α (TNF-α) has a critical role in the pathogenesis of RA, and blockade has proven to be effective in treatment of the disease. There are 3 approved anti-TNF agents, infliximab, etanercept, and adalimumab. Infliximab and etanercept have been shown to substantially and rapidly improve RA symptoms and to slow radiographic progression[1,2]. Adalimumab, a fully human anti-TNF-α monoclonal antibody, 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 (MTX), but it can be used alone when treatment with MTX is not appropriate. Several studies provide information about the combination of adalimumab with DMARD other than MTX. When used as monotherapy, the dose can be increased to 40 mg injected subcutaneously (SC) every week in case of loss of effect with the standard dose. Studies indicate that adalimumab can be effective and safe in treatment of patients with RA[3,4].

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

MATERIALS AND METHODS

Criteria for considering studies for this review

Study design. A systematic review for the Cochrane Library with quantitative metaanalysis was performed. All controlled clinical trials comparing adalimumab alone or in combination with DMARD to placebo or other DMARD were considered.

Participants. Patients with confirmed RA according to the American College of Rheumatology (ACR) 1987 revised criteria[5], which had active disease as defined in every study.

Interventions. Adalimumab 20, 40, and 80 mg given subcutaneously every week (ew) or every other week (eow), alone or in combination with DMARD versus placebo or DMARD.

Outcome measures. The primary outcome was the response rate to treatment with adalimumab as defined by the ACR[6] and the European League Against Rheumatism (EULAR) criteria[7]. Radiographic progression as measured by

From the Rheumatology Service, Hospital Universitario Virgen Macarena, Sevilla, Spain.

This review is published as a Cochrane Review in The Cochrane Library 2005, Issue 3. Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the Review.

F. Navarro-Sarabia, MD, PhD, Chair, Rheumatology Service; R. Ariza-Ariza, MD, PhD, Rheumatologist; B. Hernández-Cruz, MD, MSc, Rheumatologist; I. Villanueva, MD, PhD, Rheumatologist.

Address reprint requests to Dr. R. Ariza-Ariza, Rheumatology Service, Hospital Universitario Virgen Macarena, Avda Dr Fedriani 3, 41009 Sevilla, Spain. E-mail: rafariza@telefonica.net

Accepted for publication January 20, 2006.

the modified Sharp Index was also reported. Safety outcomes included adverse events, serious adverse events, and withdrawals due to adverse events.

Search strategy 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. The search was not limited by language, year of publication, or type of publication. In addition, the proceedings of major rheumatology conferences and reference lists from comprehensive reviews and identified clinical trials were hand searched. Content experts and Abbott Immunology were contacted to obtain additional unpublished data from published trials.

Methods of the review

Two reviewers (FNS and IVT) independently selected the trials based on title and abstract. On the selected articles, 2 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

Methodological quality was assessed by 2 reviewers independently (RAA and BHC). Disagreements were resolved by consensus. Quality was assessed according to a criteria list based on the recommendations from the Cochrane Bone, Muscle and Joint Trauma Group and a Delphi list[8,9]. These criteria included allocation concealment, methods of randomization, comparability of treatment and control groups, blinding of the outcome assessors and the subjects, definitions of the interventions and outcome measures, description of the withdrawals, and intention to treat analysis. They were coded as A (clearly yes), B (not sure), or C (clearly no). A global quality level was estimated as level A (low risk of bias, all individual criteria scored A), level B (moderate risk of bias, one or more individual criteria scored B), or level C (high risk of bias, one or more criteria scored C).

The components assessed by the Jadad scale[10] — randomization, blinding, and withdrawals and dropouts — and allocation concealment[11] were also used for assessing the methodological quality of the studies. The scale is graded from 0 to 5 and scores $\geq$ 3 mean a good methodological quality.

Grading of evidence. The evidence was graded as platinum, gold, silver, or bronze, according to the grading evidence system described by Tugwell, *et al*[12] and recommended by the Cochrane Musculoskeletal Group (website: www.cochranemsk.org).

Data extraction and analysis

Two reviewers independently extracted the data using a standardized form (RAA and BHC).

The data were analyzed using an intention to treat model. 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). 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.

RESULTS

Six studies with 2390 patients were included in this review[3,4,13-16]. All were randomized controlled trials. Keystone[13] and Weinblatt[4] compared adalimumab + MTX versus placebo + MTX. Furst[3] was a safety trial comparing adalimumab alone or in combination with DMARD versus placebo alone or with DMARD. Rau[14] compared adalimumab 1 mg/kg versus placebo. The double-blind evaluation was done in the 4 weeks after the first injection. Van de Putte 2003[15] and van de Putte 2004[16] compared adalimumab in monotherapy versus placebo. The main characteristics of these studies and the methodological quality scores are shown in Table 1. For the purposes of this review, 2 comparisons were carried out: (1) Adalimumab + MTX (or DMARD) versus placebo + MTX (or DMARD). (2) Adalimumab as monotherapy versus placebo given subcutaneously. The results with the approved doses of adalimumab (40 mg eow and 40 mg ew as monotherapy) are reported here.

Adalimumab + MTX (or DMARD) versus placebo + MTX (or DMARD)

At 24 weeks, data from 3 studies (Furst[3], Keystone[13], Weinblatt[4]) were available. The evidence level was gold. Table 2 shows the data for the ACR20/50/70 responses. Data for ACR20 response were not pooled because significant heterogeneity (chi-square 13.73, df = 2, p = 0.001) was observed. Table 3 shows data for the components of ACR responses.

At 52 weeks, data from only one study (Keystone[13]) were available. The evidence level was silver. ACR20 response was achieved by 58.93% of the patients taking adalimumab versus 24% of placebo patients, with an absolute risk difference of 34.93% (risk difference 0.35, 95% CI 0.26–0.44). The relative risk was 2.46 (95% CI 1.87–3.22) with NNT = 2.9.

ACR50 response was achieved by 41.54% of adalimumab patients versus 9.5% of placebo patients, with an absolute risk difference of 32.04% (risk difference 0.32, 95% CI 0.24–0.40). The relative risk was 4.37 (95% CI 2.77–6.91) with NNT = 3.1.

ACR70 response was achieved by 23.18% of adalimumab patients versus 4.5% of placebo patients, with an absolute risk difference of 18.68% (risk difference 0.19, 95% CI 0.12–0.25). The relative risk was 5.15 (95% CI 2.60-10.22) with NNT = 5.3.

Table 4 shows data for components of the ACR response.

The available data for radiological outcomes included 355 patients. The change in the modified Sharp Index was 0.10 (SD 4.80) in the adalimumab patients versus 2.70 (SD 6.80) in placebo patients, with an absolute benefit of –2.60 and a relative difference of 3.91%. The weighted mean difference was –2.60 (95% CI –3.83 to –1.37).

The change in the erosion score was 0.00 (SD 2.80) in the adalimumab patients versus 1.60 (SD 4.40) in placebo patients, with an absolute benefit of –1.60 and a relative difference of 4.30%. The weighted mean difference was –1.60 (95% CI –2.37 to –0.83).

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

Safety. All studies included in this review and all data were analyzed taking into account all doses of adalimumab and all periods of treatment. Significant differences between adali-

Table 1. Main characteristics of studies included in the review.

Study	n	Duration, weeks	Interventions	Outcomes	Methodological Quality
Furst 2003[3]	623	24	Adalimumab 40 mg eow (+ DMARD) vs placebo (+ DMARD)	Safety ACR response	Quality level: B Evidence level: silver Jadad: 3 Allocation concealment unclear. Randomization and blinding not described
Keystone 2004[13]	619	52	Adalimumab 40 mg eow or 20 mg ew + MTX vs placebo + MTX	ACR response and its components Radiographic progression	Quality level B Evidence level: silver Jadad:3 Allocation concealment unclear. Randomization and blinding not described
Rau 2004[14]	36	4	Adalimumab 1 mg/kg + MTX vs placebo + MTX, once	ACR response and its components EULAR response	Quality level B Evidence level: silver Jadad: 3 Allocation concealment unclear. Randomization and blinding not described
Van de Putte 2003[15]	284	12	Adalimumab 20, 40, or 80 mg ew vs placebo	ACR response and its components DAS28	Quality level B Evidence level: silver Jadad: 3 Allocation concealment unclear. Randomization and blinding not described
Van de Putte 2004[16]	544	26	Adalimumab 20 mg ew, 40 mg ew or eow vs placebo	ACR response and its components EULAR response DAS28	Quality level A Evidence level: gold Jadad: 5 Allocation concealment adequate
Weinblatt 2003[4]	271	24	Adalimumab 20, 40, or 80 mg eow + MTX vs placebo + MTX	ACR response and its components	Quality level A Evidence level: gold Jadad: 4 Blinding procedure not described Allocation concealment adequate

* Double-blind evaluation was done in the 4th week after the injection. There was an open-label extension. An arm with intravenous adalimumab was also studied but it was not included in this review. MTX: methotrexate; DMARD: drug modifying antirheumatic drugs; ew: every week; eow: every other week. Descriptions of the outcomes and quality scores in the text. Quality level A/B: low/moderate risk of bias as described in the text. Evidence levels defined in the text.

mumab and placebo patients were found only in the rate of positive antinuclear antibodies (ANA) and anti-DNA antibodies and in the frequency of serious infections in the longer study (Keystone[13]; Table 5). In this study, 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 0.03, 95% CI 0.01–0.05. The relative risk was 7.64 (95% CI 1.02–57.18) with NNH = 30.2.

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 of 0.06 (95% CI 0.01–0.10). The relative risk was 1.60 (95% CI 1.20–2.13) with NNH = 15.0 (95% CI 8.0–43.0).

The global rates of positive anti-DNA antibodies were 9.46% in the adalimumab patients versus 0.73% in placebo patients, with a weighted risk difference of 0.09 (95% CI 0.03–0.15). The relative risk was 11.07 (95% CI 4.05–30.31) with NNH = 14.0 (95% CI 5.0–45.0).

Adalimumab versus placebo

Only results at 24/26 weeks are reported here. Data for adalimumab 40 mg ew were available from only one study (van de Putte 2004[16]). The evidence level was gold. An ACR20 response was achieved by 53.39% of the adalimumab patients versus 19.10% of placebo patients, with an absolute risk difference of 34.29% (risk difference 0.34, 95% CI 0.22–0.46). The relative risk was 2.80 (95% CI 1.83–4.28) with NNT = 2.9. An ACR50 response was achieved by 34.95% of the adal-

Table 2. Adalimumab 40 mg eow + MTX (or DMARD) vs placebo + MTX (or DMARD). ACR 20/50/70 at 24 weeks.

	Study	Adalimumab, %	Control, %	Risk Difference** (95% CI)	Relative Risk (95% CI)	NNT (95% CI)
ACR20*	Furst 2003	55.63	35.18	0.18 (0.10–0.27)	1.52 (1.25–1.86)	5.4
	Weinblatt 2003	67.16	14.5	0.53 (0.38–0.67)	4.63 (2.47–8.66)	1.9
	Keystone 2004	63.28	29.5	0.34 (0.25–0.43)	2.15 (1.69–2.72)	3.0
ACR50	Furst 2003	29.50	11.85	0.18 (0.11–0.24)	2.49 (1.71–3.62)	5.7
	Weinblatt 2003	55.22	8.06	0.47 (0.33–0.61)	6.85 (2.88–16.31)	2.1
	Keystone 2004	39.13	9.5	0.30 (0.22–0.37)	4.12 (2.60–6.53)	3.4
	Pooled data	36.44	10.52	0.30 (0.16–0.45)	3.73 (2.21–6.29)	4.0 (3.0–8.0)
ACR70	Furst 2003	14.17	3.70	0.10 (0.06–0.15)	3.83 (1.94–7.54)	9.6
	Weinblatt 2003	26.86	4.83	0.22 (0.10–0.34)	5.55 (1.72–17.93)	4.5
	Keystone 2004	20.77	2.50	0.18 (0.12–0.24)	8.31 (3.36–20.55)	5.5
	Pooled data	18.31	3.38	0.16 (0.09–0.23)	5.14 (3.14–8.41)	7.0 (5.0–13.0)

* Data were not pooled due to significant heterogeneity (chi-square 13.73, df = 2, p = 0.001). ** The difference of absolute risk for the outcome between NNT: number needed to treat.

Table 3. Adalimumab 40 mg eow + MTX vs placebo + MTX. Components of the ACR response at 24 weeks.

	Study	Mean Change, Adalimumab (SD)	Mean Change, Control (SD)	Absolute Benefit	Relative Difference, %	Weighted Mean Difference (95% CI)
Tender joints	Weinblatt 2003	–14.40 (18.40)	–5.30 (12.10)	–9.10	31.7	–9.10 (–14.44 to –3.76)
Pooled WMD (95% CI) –6.68 (–9.02 to – 4.34)	Keystone 2004	–15.40 (12.30)	–9.30 (14.40)	–6.10	21.7	–6.10 (–8.71 to –3.49)
Swollen joints	Weinblatt 2003	–10.40 (10.00)	–2.90 (10.50)	–7.50	44.37	–7.50 (–11.04 to –3.96)
Pooled WMD (95% CI) –5.86 (–7.90 to –3.82)	Keystone 2004	–11.10 (9.70)	–5.90 (10.60)	–5.20	27.36	–5.20 (–7.18 to –3.22)
Patient pain assesment	Weinblatt 2003	25.10 (33.10)	–8.60 (22.50)	–16.5	28.84	–16.50 (–26.20 to –6.80)
Pooled WMD (95% CI) –15.79 (–20.27 to –11.32)	Keystone 2004	–28.20 (25.80)	–12.60 (26.10)	–15.6	27.71	–15.60 (–20.64 to –10.56)
Patient global	Weinblatt 2003	–29.70 (31.80)	–8.60 (25.10)	–21.1	36.37	–21.10 (–30.95 to –11.25)
Pooled WMD (95% CI) –17.01 (–21.71 to –12.31)	Keystone 2004	–27.20 (26.90)	–11.40 (28.10)	–15.8	29.10	–15.80 (–21.15 to –10.45)
Physician global	Weinblatt 2003	–31.10 (29.40)	–6.80 (24.50)	–24.3	41.25	–24.30 (–32.83 to –15.77)
Pooled WMD (95% CI) –19.42 (–27.19 to –11.65)	Keystone 2004	–37.30 (21.60)	–21.10 (25.30)	–16.2	26.42	–16.20 (–20.78 to –11.62)
HAQ	Weinblatt 2003	–0.62 (0.63)	–0.27 (0.57)	–0.35	21.34	–0.35 (–0.56 to –0.14)
Pooled WMD (95% CI) –0.33 (–0.42 to –0.20)	Keystone 2004	–0.56 (0.52)	–0.24 (0.52)	–0.32	21.62	–0.32 (–0.42 to –0.22)
CRP	Weinblatt 2003	–1.60 (1.60)	0.10 (2.40)	–1.70	54.83	–1.70 (–2.41 to –0.99)
Pooled WMD (95% CI)* –1.21 (–2.09 to – 0.33)	Keystone 2004	–1.00 (2.90)	–0.20 (1.90)	–0.80	44.44	–0.80 (–1.27 to – 0.33)

* Test for heterogeneity showed chi-square = 4.27, df = 2, p = 0.04. WMD: weighted mean difference. HAQ: Health Assessment Questionnaire; CRP: C-reactive protein.

imumab patients versus 8.18% of placebo patients, with an absolute risk difference of 26.77% (risk difference 0.27, 95% CI 0.16–0.37). The relative risk was 4.27 (95% CI 2.17–8.43) with NNT = 3.7. An ACR70 response was achieved by 18.44% of the adalimumab patients versus 1.81% of placebo patients, with an absolute risk difference of 16.63% (risk difference 0.17, 95% CI 0.09–0.25). The relative risk was 10.15 (95% CI 2.42–42.18) with NNT = 6.0. An at least moderate EULAR response was achieved by 63.10% of the adalimumab patients versus 26.36% of placebo patients, with an absolute risk difference of 36.74% (risk difference 0.37, 95% CI 0.24–0.49). The relative risk was 2.39 (95% CI 1.69–3.38) with NNT = 2.7.

Table 4. Adalimumab 40 mg eow + MTX vs placebo + MTX. Components of the ACR response at 52 weeks (Keystone 2004).

	Mean Change, Adalimumab (SD)	Mean Change, Control (SD)	Absolute Benefit	Relative Difference, %	Weighted Mean Difference (95% CI)
Tender joints	–16.60 (12.80)	–9.60 (14.60)	–7.00	24.9	–7.00 (–9.68 to – 4.32)
Swollen joints	–11.90 (11.00)	–5.60 (10.30)	–6.30	33.15	–6.30 (–8.37 to –4.23)
Patient pain assessment	–29.40 (26.40)	–11.20 (27.70)	–18.20	32.32	–18.20 (–23.46 to –12.94)
Patient global assessment	–27.50 (28.40)	–19.90 (30.40)	–16.60	30.57	–16.60 (–22.32 to –10.88)
Physician global assessment	–39.40 (22.20)	–19.50 (25.80)	–19.90	32.6	–19.90 (–24.58 to –15.22)
HAQ	–0.59 (0.57)	–0.25 (0.56)	–0.34	22.97	–0.34 (–0.45 to –0.23)
CRP	–0.70 (1.70)	–0.10 (1.90)	–0.60	33.33	–0.60 (–0.93 to –0.27)

HAQ: Health Assessment Questionnaire; CRP: C-reactive protein.

Table 5. Safety of adalimumab: serious infections and positive antinuclear antibodies (ANA).

	Outcome	Data Source	Adalimumab, %	Control, %	Risk Difference* (95% CI)	Relative Risk (95% CI)	NNH
Adalimumab in combination	Serious infections**	Furst 2003	1.53	2.22	NS	0.69 (0.20–2.42)	—
		Keystone 2004	3.81	0.5	0.03 (0.01–0.05)	7.64 (1.02–57.18)	30.2
	Positive ANA	Pooled data	16.10	11.78	0.06 (0.01–0.10)	1.60 (1.20–2.13)	15.0
Adalimumab in monotherapy	Serious infections	Pooled data	1.98	0	NS	NS	
	Positive ANA	Pooled data	23.64	17.77	0.07 (0.88–2.55)	1.50 (0.88–2.55)	11.0

* The difference of absolute risk for the outcome between the 2 groups (adalimumab and control), as calculated by RevMan. ** Data were not pooled due to significant heterogeneity.

Table 6. Adalimumab 40 mg ew and eow vs placebo. DAS28 and components of the ACR response at 26 weeks (van de Putte 2004).

	Mean Change, Adalimumab (SD)	Mean Change, Control (SD)	Absolute Benefit	Relative Difference, %	Weighted Mean Difference (95% CI)
DAS28					
40 mg ew	–2.00 (1.60)	–0.70 (1.30)	–1.30	18.31	–1.30 (–1.69 to –0.91)
40 mg eow	–1.70 (1.60)	–0.70 (1.30)	–1.00	14.08	–1.00 (–1.38 to –0.62)
Tender joints					
40 mg ew	–17.10 (15.50)	–6.60 (16.60)	–10.50	29.57	–10.50 (–4.81 to –6.19)
40 mg eow	–13.60 (18.70)	–6.60 (16.60)	–7.00	19.71	–7.00 (–11.64 to –2.36)
Swollen joints					
40 mg ew	–8.30 (10.80)	–2.40 (9.50)	–5.90	29.79	–5.90 (–8.64 to –3.16)
40 mg eow	–8.50 (10.60)	–2.40 (9.50)	–6.10	30.80	–6.10 (–8.74 to – 3.46)
Patient pain assessment					
40 mg ew	–32.00 (31.30)	–11.00 (26.70)	–21.00	29.91	–21.00 (–29.84 to –13.16)
40 mg eow	–27.60 (31.10)	–11.00 (26.70)	–16.60	23.64	–16.60 (–24.20 to –20)
Patient global					
40 mg ew	–35.00 (31.50)	–10.60 (27.80)	–24.40	33.98	–24.40 (–31.40 to –16.40)
40 mg eow	–27.90 (30.50)	–10.60 (27.80)	–17.30	24.09	–17.30 (–24.96 to –9.64)
Physician global					
40 mg ew	–32.50 (27.30)	–10.90 (25.40)	–21.60	31.53	–21.60 (–28.69 to –14.51)
40 mg eow	–27.30 (28.80)	–10.90 (25.40)	–16.40	23.94	–16.40 (–23.52 to –9.28)
HAQ					
40 mg ew	–0.49 (0.54)	–0.07 (0.49)	–0.42	22.34	–0.42 (–0.56 to –0.28)
40 mg eow	–0.38 (0.60)	–0.07 (0.49)	–0.31	16.49	–0.31 (–0.45 to –0.17)

ew: every week; eow: every other week; DAS28: Disease Activity Score 28; HAQ: Health Assessment Questionnaire.

A good EULAR response was achieved by 13.59% of the adalimumab patients versus 3.63% of placebo patients, with an absolute risk difference of 9.96% (risk difference 0.10, 95% CI 0.02–0.17). The relative risk was 3.74 (95% CI 1.27–10.99) with NNT = 10.0. Data for components of the ACR response are shown in Table 6.

Data for adalimumab 40 mg eow were available from 2 studies (van de Putte 2004[16], Furst[3]) with an evidence level gold. An ACR20 response was achieved by 47.05% of the adalimumab patients versus 23.41% of placebo patients, with a weighted risk difference of 0.24 (95% CI 0.14–0.34). The relative risk was 1.91 (95% CI 1.17–3.10) with NNT = 5.0 (95% CI 3.0–9.0). An ACR50 response was achieved by 23.53% of the adalimumab patients versus 8.22% of placebo patients, with a weighted risk difference of 0.15 (95% CI 0.08–0.23). The relative risk was 2.84 (95% CI 1.58–5.12) with NNT = 7.0 (95% CI 4.0–20.0). An ACR70 response was achieved by 14.11% of the adalimumab patients versus 1.89% of placebo patients, with a weighted risk difference of 0.12 (95% CI 0.06–0.18). The relative risk was 7.33 (95% CI 2.25–23.90) with NNT = 9.0 (95% CI 3.0–38.0). In van de Putte 2004[16], an at least moderate EULAR response was achieved by 55.75% of the adalimumab patients versus 26.36% of placebo patients, with an absolute risk difference of 29.39% (risk difference 0.29, 95% CI 0.17–0.42). The relative risk was 2.11 (95% CI 1.49–3.01) with NNT = 3.4. In van de Putte 2004[16], a good EULAR response was achieved by 8.85% of the adalimumab patients versus 3.63% of placebo patients, with an absolute risk difference of 5.22% (risk difference 0.05, 95% CI –0.01 to 0.12). The relative risk was 2.43 (95% CI 0.79–7.53). Data for the Disease Activity Score 28 (DAS28) and the ACR response components were only available in van de Putte 2004[16] (Table 6).

Safety. Data were analyzed considering all doses of adalimumab and all periods of treatment. Data about adverse events were available in Furst[3] and van de Putte 2004[16], including 676 patients. In Furst[3], 80.7% of the adalimumab patients had any adverse events versus 48% of placebo patients, with an absolute risk difference of 32.7% (risk difference 0.33, 95% CI 0.17–0.48). The relative risk was 1.68 (95% CI 1.29–2.20) with NNH = 3.0. In van de Putte 2004[16], 98.84% of the adalimumab patients had any adverse events versus 95.45% of placebo patients (no significant difference). Significant heterogeneity was found, thus data were not pooled. The most frequent adverse events were upper respiratory tract infections, rhinitis, and headache. No significant differences were found between adalimumab and placebo patients for serious adverse events, withdrawals due to adverse events, infections, and serious infections. In both studies, 23.64% of the adalimumab patients had positive ANA versus 17.77% of placebo patients, with a weighted risk difference of 0.07 (95% CI 0.02–0.12). The relative risk was 1.50 (95% CI 0.88–2.55) with NNH = 11.0 (95% CI 6.0–87.0).

DISCUSSION

We performed a systematic review of the efficacy and safety of adalimumab. This metaanalysis supports the efficacy, at 24 and 52 weeks' treatment, of adalimumab in combination with MTX measured by the ACR core set response. At 24 weeks, the NNT to achieve an ACR20/50/70 with SC adalimumab 40 mg eow ranged from 1.89 to 7. The doses of 20 mg ew and 80 mg eow had similar efficacy compared to the approved dose (data not shown). At 52 weeks, the NNT to achieve an ACR20/50/70 with adalimumab 40 mg eow ranged from 2.86 to 5.35, and the radiological progression was significantly slower.

This review also supports the short-term efficacy of adalimumab monotherapy. At 24/26 weeks, the NNT to achieve an ACR20/50/70 with adalimumab 40 mg eow ranged from 5 to 9. The frequency of positive ANA was somewhat higher with adalimumab in monotherapy than in studies of combinations with MTX, although the risk differences were similar. It remains uncertain if a developing resistance mechanism could explain the greater efficacy of adalimumab combined with MTX than adalimumab used as monotherapy.

The other approved anti-TNF agents, infliximab and etanercept, have also demonstrated clinical efficacy and a favorable effect on radiographic progression in patients with RA. Although there have been no comparative studies between anti-TNF agents, efficacy patterns seem to be similar. However, there are studies that show efficacy of infliximab and etanercept in early RA, whereas studies with adalimumab involve RA patients with long-standing disease and failure with previous DMARD.

The safety profile of adalimumab appears similar to the other biologics, with no significant differences versus control groups in most of the items considered, but positive ANA are consistently more common in adalimumab patient groups, even though they are not clinically relevant. Serious infections were significantly more frequent with adalimumab in combination with MTX in the longer study, Keystone[13], with a NNH of 30.21. Until adalimumab is used widely we will not know if it has the same problems with tuberculosis and fungal infections that are seen with infliximab and etanercept.

The level of evidence of the conclusions we studied ranged from silver to gold and there were no conclusions with a platinum level of evidence. This was due to 2 main reasons: first, the number of studies of adalimumab was limited and many different doses were administered. In many cases, i.e., radiographic outcomes, data were only available from one study and pooling was not possible. Second, although all studies had acceptable methodological quality, some did not meet all criteria for a gold level for evidence. This was mainly because allocation concealment was not clearly described in some studies. In summary, on the basis of the studies reviewed here, it can be said that adalimumab in combination with methotrexate or in monotherapy is efficacious and safe in treatment of RA. Longterm efficacy and safety studies are

needed. The efficacy and the effect on radiographic progression of adalimumab in patients with early RA and in DMARD-naive patients remain to be assessed.

REFERENCES

1. Blumenauer B, Judd M, Wells G, et al. Infliximab for the treatment of rheumatoid arthritis. In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons Publishers.
2. Blumenauer B, Judd M, Cranney A, et al. Etanercept for the treatment of rheumatoid arthritis. In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons Publishers.
3. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis. Results of the Safety Trial of Adalimumab in Rheumatoid Arthritis. J Rheumatol 2003;30:2563-71.
4. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate. The ARMADA trial. Arthritis Rheum 2003;48:33-45.
5. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
6. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
7. Van Gestel AM, Prevoo ML, van t'Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism. Arthritis Rheum 1996;39:34-40.
8. Clarke M, Oxman AD, editors. The Cochrane Library, Issue 2, 2001.
9. Verhagen AP, Vet HC, de Bie RA, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic review developed by Delphi consensus. J Clin Epidemiol 1998;51:1235-41.
10. Jadad AR, Moore RA, Carroll D, et al. assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17:1-12.
11. Schultz KF. Subverting randomization in controlled trials. JAMA 1995;274:1456-8.
12. Tugwell P, Shea B, Boers M, Brooks P, Simon L, Strand V, Wells G, editors. Evidence-based rheumatology. London: BMJ Books; 2004.
13. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumour necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy. A randomized, placebo-controlled, 52 weeks trial. Arthritis Rheum 2004;50:1400-11.
14. Rau R, van Riel PLCM, van de Putte LBA, et al. Rapid alleviation of signs and symptoms of rheumatoid arthritis with intravenous or subcutaneous administration of adalimumab in combination with methotrexate. Scand J Rheumatol 2004;33:145-53.
15. van de Putte LBA, Rau R, Breedveld FC, et al. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E27) in DMARD refractory patients with rheumatoid arthritis: a 12 weeks, phase II study. Ann Rheum Dis 2003;62:1168-77.
16. van de Putte LBA, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 2004;63:508-16.