EXTENDED REPORT

Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial

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Objective: To evaluate the safety and effectiveness of adalimumab alone or in combination with standard disease-modifying antirheumatic drugs (DMARDs) for the treatment of rheumatoid arthritis (RA).

Methods: Patients with active RA despite treatment with DMARDs or prior treatment with a tumour necrosis factor antagonist participated in a multicentre, open-label clinical study of adalimumab 40 mg every other week for 12 weeks with an optional extension phase. Patients were allowed to continue with pre-existing traditional DMARDs. Long-term safety results are reported for all patients (4210 patient-years (PYs) of adalimumab exposure). The observed effectiveness results at week 12 are reported using American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) response criteria.

Results: Among the 6610 treated patients, adalimumab was generally well tolerated. Serious infections occurred in 3.1% of patients (5.5/100 PYs, including active tuberculosis, 0.5/100 PYs). Demyelinating disease (0.06%) and systemic lupus erythematosus (0.03%) were rare serious adverse events. The standardised incidence ratio of malignancy was 0.71 (95% CI 0.49 to 1.01). The standardised mortality ratio was 1.07 (95% CI 0.75 to 1.49). At week 12, 69% of patients achieved an ACR20 response, 83% a moderate, and 33% a good EULAR response. Adalimumab was effective in combination with a variety of DMARDs. The addition of adalimumab to antimalarials was comparably effective to the combination of adalimumab and methotrexate.

Conclusions: Considering the limitations of an open-label study, adalimumab alone or in combination with standard DMARDs appeared to be well tolerated and effective in 6610 difficult-to-treat patients with active RA treated in clinical practice.

Tumour necrosis factor (TNF) antagonists are effective in the treatment of rheumatoid arthritis (RA), particularly when combined with methotrexate (MTX).[1–3] However, a detailed assessment of TNF antagonist therapy in combination with the wide range of traditional disease-modifying antirheumatic drugs (DMARDs) commonly used to treat patients with RA in clinical practice is lacking.[4–13]

The ReAct (Research in Active Rheumatoid Arthritis) study was initiated to assess the safety and effectiveness of adalimumab, a fully human IgG_1 anti-TNF monoclonal antibody (1) in combination with a variety of DMARDs and DMARD combinations and (2) in patients previously treated with etanercept or infliximab. The open-label design limits the strength of the conclusions that can be drawn from the data, but allowed the collection of data from more than 6000 patients with RA being treated in a variety of clinical practice settings. Because this was not a randomised, placebo-controlled design to compare the effect of adalimumab with placebo, the term ''effectiveness'' is used. Safety data for the entire study period and an overview of adalimumab effectiveness in combination with various DMARDs from the initial 12 weeks of the study are presented here. A detailed analysis for patients who were previously treated with etanercept or infliximab will be reported separately.

METHODS

Patients

Eligible patients were men and women ⩾18 years of age with active, adult-onset RA in accordance with the 1987 revised criteria of the American College of Rheumatology (ACR).[14] Inclusion criteria required a disease duration of ⩾3 months, a Disease Activity Score based on erythrocyte sedimentation rate and an evaluation of 28 joints (DAS28) of ⩾3.2,[15] and treatment failure with at least one traditional DMARD. Exclusion criteria included: current pregnancy or breast feeding; any persistent or severe infection within 30 days of baseline; previous treatment with other TNF antagonists up to 2 months before enrolment; treatment with alkylating agents, total lymphoid irradiation, intravenous immunoglobulin or any investigational biologic agent; a history of active arthritis other than RA; any uncontrolled

Abbreviations: ACR, American College of Rheumatology; AE, adverse event; AM, antimalarials; AZA, azathioprine; CsA, ciclosporin; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; HAQ DI, Health Assessment Questionnaire Disability Index; LEF, leflunomide; MTX, methotrexate; PY, patient-year; RA, rheumatoid arthritis; SAE, serious adverse event; SEER, Surveillance, Epidemiology, and End Results; SIR, standardised incidence ratio; SSZ, sulfasalazine; TB, tuberculosis; TNF, tumour necrosis factor

medical condition; a history or signs of demyelinating disease; active tuberculosis (TB) or histoplasmosis; malignancy (except for completely treated squamous or basal cell carcinoma).

All patients underwent Mantoux testing for latent TB. A skin induration ⩾5 mm was considered a positive result by the investigator unless national guidelines required a different threshold. Adequate treatment in accordance with national guidelines had to be initiated for latent TB before the first injection of adalimumab unless proper prior treatment for TB was documented.

All study centres received approval from independent ethics committees and conducted the study in accordance with principles of the Declaration of Helsinki. Each patient gave written informed consent before any study-related procedures were performed.

Procedures

ReAct was a 12-week, open-label, multicentre study with an optional extension phase until adalimumab became commercially available. Patients could enter a subsequent postmarketing observational study of adalimumab for up to 5 years. The dosage regimen was a subcutaneous injection of adalimumab 40 mg (Abbott Laboratories, Abbott Park, Illinois, USA) every other week. Patients were allowed to continue treatment with DMARDs (defined as MTX, leflunomide (LEF), sulfasalazine (SSZ), chloroquine or hydroxychloroquine (antimalarials, AM), azathioprine (AZA), and parenteral or oral gold) or any combination of DMARDs, glucocorticoids (prednisone equivalent ⩽10 mg/day), and non-steroidal anti-inflammatory drugs if the treatment regimens were not modified until week 12. Ciclosporin (CsA) was not allowed as a concomitant DMARD as a general precaution against excessive immunosuppression.

Safety, including physical examinations, laboratory measurements and adverse event (AE) reports, and effectiveness were evaluated at weeks 2, 6, 12, and every 8 weeks thereafter. Measures of effectiveness were: ACR 20% (ACR20), 50% (ACR50) and 70% (ACR70) improvement responses;[16] European League Against Rheumatism (EULAR) responses;[17] changes in DAS28; and changes in ACR component variables, including the Health Assessment Questionnaire Disability Index (HAQ DI).[18]

Statistical analysis

Patients who received at least one adalimumab injection were included in all analyses. The duration of adalimumab exposure was defined as the number of days from the first to the last injection plus 14 days.

Subgroup analyses were performed for patients receiving adalimumab monotherapy (defined as no concomitant DMARD irrespective of combination with glucocorticoids or non-steroidal anti-inflammatory drugs) versus combination therapy with at least one DMARD. Patients were further stratified by: the number of concomitant DMARDs (one, two, three or more); the specific single DMARD (defined as exclusive treatment with MTX, LEF, SSZ, AM, or a single other DMARD not previously listed); the DMARD combinations (ie, MTX+LEF, MTX+AM, MTX+SSZ, and MTX+SSZ+AM). Safety analyses for all patients and for the major subsets without versus with concomitant DMARD therapy were performed for the complete treatment period (up to 70 days (five half-lives) after the last adalimumab injection), whereas analyses of the detailed DMARD subgroups were limited to the first 12 weeks of treatment, during which changes in DMARD therapy were not allowed.

A multiple Cox proportional hazards model was used to assess possible predictors of serious infection. The following potential predictors at baseline of serious infection were specified a priori: age (years); sex; medical history of diabetes mellitus, cardiac or pulmonary disease; tobacco use (ever); duration of RA (years); number of previous DMARDs; previous anti-TNF treatment; rheumatoid factor (+/−); DAS28; HAQ DI score; C-reactive protein concentration; leucopenia (<3.5/nl); glucocorticoid use; and LEF use.[19–21]

The standardised mortality ratio was calculated using the most recent World Health Organization Statistical Information System (WHOSIS) data for the 12 countries where ReAct was conducted.[22] The standardised incidence ratio (SIR) of the observed malignancies in ReAct was determined by comparison with the expected number of cancers in a cohort matched for age and sex using the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database in place of the multinational European cancer database.[23]

Effectiveness data are presented as observed values at week 12. The mean changes in DAS28, HAQ DI scores, and tender

Table 1 Baseline characteristics of the patients

Concomitant DMARD group	Age (years)	Female (%)	RF+ (%)	Disease duration (years)	Prior DMARDs (n)	Glucocorticoid use (%)	DAS28	HAQ DI, 0−3	TJC, 0−28	SJC, 0−28	CRP (mg/l)
All patients (n = 6610)	54 (13)	81	73	11 (9)	3.0 (1.8)	71	6.0 (1.1)	1.64 (0.68)	14 (7)	10 (6)	26 (31)
Number of concomitant DMARDs											
No DMARDs (n = 1731)	55 (13)	82	72	12 (9)	3.1 (2.1)	70	6.2 (1.1)	1.73 (0.68)	14 (7)	11 (6)	29 (35)
⩾1 DMARD (n = 4879)	53 (13)	80	73	10 (8)	2.9 (1.7)	72	6.0 (1.1)	1.60 (0.68)	13 (7)	10 (6)	25 (29)
1 DMARD (n = 4004)	53 (13)	81	73	10 (8)	2.8 (1.7)	71	6.0 (1.1)	1.61 (0.68)	13 (7)	10 (6)	24 (28)
2 DMARDs (n = 769)	53 (13)	75	74	9 (7)	3.3 (1.5)	75	6.0 (1.1)	1.55 (0.69)	13 (7)	11 (6)	27 (32)
⩾3 DMARDs (n = 106)	52 (12)	76	76	10 (9)	3.8 (1.2)	67	5.9 (1.1)	1.68 (0.65)	13 (7)	12 (7)	32 (43)
One exclusive concomitant DMARD											
MTX only (n = 2794)	53 (13)	82	73	10 (8)	2.7 (1.7)	70	6.0 (1.1)	1.61 (0.68)	13 (7)	10 (6)	23 (27)
LEF only (n = 842)	54 (12)	82	75	11 (9)	3.3 (1.7)	73	6.0 (1.1)	1.58 (0.68)	13 (7)	11 (6)	24 (28)
SSZ only (n = 133)	56 (13)	81	69	11 (8)	3.1 (1.8)	63	6.1 (1.1)	1.70 (0.71)	14 (8)	11 (6)	30 (32)
AM only (n = 148)	56 (12)	83	74	8 (7)	2.8 (1.8)	78	6.2 (1.0)	1.62 (0.69)	15 (7)	10 (6)	28 (30)
1 other DMARD* (n = 84)	55 (13)	79	68	13 (9)	4.1 (2.1)	81	6.3 (1.0)	1.87 (0.69)	14 (7)	11 (5)	30 (33)
DMARD combinations											
MTX+LEF (n = 180)	53 (13)	79	72	10 (8)	3.5 (1.6)	81	6.1 (1.0)	1.55 (0.64)	13 (7)	11 (6)	27 (35)
MTX+AM (n = 269)	52 (13)	75	76	8 (7)	2.9 (1.4)	74	6.0 (1.1)	1.52 (0.7)	14 (7)	10 (6)	23 (27)
MTX+SSZ (n = 182)	52 (13)	70	72	9 (8)	3.0 (1.3)	69	5.9 (1.1)	1.57 (0.7)	13 (7)	11 (6)	28 (33)
MTX+SSZ+AM (n = 76)	53 (12)	78	71	9 (8)	3.7 (1.2)	66	5.9 (1.2)	1.69 (0.66)	13 (8)	12 (7)	37 (46)

AM, antimalarials; AZA, azathioprine; CRP, C-reactive protein; CsA, ciclosporin; DAS28, Disease Activity Score 28; DMARDs, disease-modifying antirheumatic drugs; HAQ DI, Health Assessment Questionnaire Disability Index; LEF, leflunomide; MTX, methotrexate; RF+, rheumatoid factor positive; SJC, swollen joint count; SSZ, sulfasalazine; TJC, tender joint count.
Data are mean (SD) unless otherwise noted.
*Of these 84 patients, 51% were receiving AZA, 27% were receiving parenteral gold, 17% were receiving CsA, and 5% were receiving penicillamine.

Table 2 Selected serious adverse events per 100 patient-years (100 PYs) by subgroup*

	All patients (n = 6610) PYs = 4210	No concomitant DMARDs (n = 1731) PYs = 1041	Concomitant DMARDs (n = 4879) PYs = 3169
All serious adverse events	28.4	40.0	24.6
Blood and lymphatic system disorders*	0.5	1.2	0.3
Anaemias (non-haemolytic and marrow depression)†	0.4	0.9	0.3
Cardiac disorders*	1.4	1.9	1.3
Heart failures†	0.4	0.8	0.3
Gastrointestinal disorders*	1.4	1.8	1.2
General disorders and administration site conditions*	1.5	1.9	1.4
Hepatobiliary disorders*	0.4	0.8	0.3
Immune system disorders*	0.2	0.4	0.2
Allergic conditions†	0.2	0.4	0.2
Infections and infestations*	5.5	6.6	5.1
Lower respiratory tract and lung infections‡	1.0	1.2	1.0
Abdominal and gastrointestinal infections‡	0.4	1.0	0.2
Sepsis, bacteraemia and viraemia‡	0.4	0.5	0.4
Bone and joint‡	0.1	0.2	0.1
Injury, poisoning and procedural complications*	2.1	3.3	1.7
Musculoskeletal and connective tissue disorders*	6.9	11.0	5.5
Joint disorders†	5.3	8.5	4.3
Neoplasm benign, malignant, and unspecified (including cysts and polyps)*	1.1	1.3	1.0
Malignancy§	1.1	1.2	1.0
Nervous system disorders*	1.3	1.7	1.2
Renal and urinary disorders*	0.5	0.6	0.5
Reproductive system and breast disorders*	0.4	0.8	0.3
Respiratory, thoracic, and mediastinal disorders*	1.3	1.3	1.3
Parenchymal lung disorders (not elsewhere classified)‡	0.2	0.3	0.2
Skin and subcutaneous tissue disorders*	0.5	0.8	0.4
Surgical and medical procedures*	1.1	0.9	1.1
Vascular disorders*	0.8	1.0	0.8

DMARDs, disease-modifying antirheumatic drugs; MedDRA, Medical Dictionary for Regulatory Activities.
*MedDRA System Organ Class term.
†MedDRA High Level Group term.
‡MedDRA High Level term.
§Includes all neoplasms not explicitly reported as benign.

and swollen joint counts from baseline to week 12 were analysed by paired *t* test. Adjustment for baseline differences between treatment subgroups was performed with the combination of adalimumab and MTX as the reference group. Logistic regression analyses were used for the following dichotomous end points: ACR20, 50, 70 responses, moderate and good EULAR responses, and DAS28. Possible confounders were identified as age (years), sex, duration of RA (years), baseline DAS28, baseline HAQ DI score, number of previous DMARDs, and comorbidities (none or one versus two or more). The number of baseline comorbidities was identified during the medical history review of gastrointestinal, cardiovascular, metabolic, genitourinary, neurological and psychiatric, pulmonary, and whole body disorders.

RESULTS

Patient disposition and withdrawals

Of 6610 patients enrolled at 448 study centres in 12 countries, 3721 (56.3%) were treated in hospital-based clinics, 2428 (36.7%) in university-based hospitals, and 461 (7.0%) in private practice. At week 12, 93% (6140) of 6610 enrolled patients continued in the study; 4.3% withdrew because of AEs and 1.4% because of lack of adalimumab effectiveness. During the complete adalimumab treatment period, 10.3% (682) of 6610 patients withdrew because of AEs and 6.8% (450) because of lack of adalimumab effectiveness. The number of patients over time was 6538 (week 2), 6218 (week 6), 6140 (week 12), 5230 (week 20), 4119 (week 28), 3021 (week 36), 1251 (week 52), and 702 (week 60), with a mean/median adalimumab exposure of 233/211 days (maximum 669 days).

Baseline patient characteristics

Table 1 summarises baseline patient characteristics. Although CsA was an excluded DMARD, 25 patients received CsA concomitantly, and data for these patients were included in all analyses. Before study entry, MTX, LEF, AM, SSZ, parenteral gold, CsA and infliximab had been prescribed for 89%, 42%, 42%, 39%, 28%, 16% and 11%, respectively, of all enrolled

Table 3 Independent predictors for serious infection

Variable	Type of variable (continuous or dichotomous)	Hazard ratio	95% CI	p Value
Pulmonary disease	Yes versus no	1.53	1.14 to 2.06	<0.0048
Male sex	Yes versus no	1.48	1.07 to 2.06	<0.0187
HAQ DI score (points)	Continuous	1.42	1.14 to 1.77	<0.0017
Cardiac disease	Yes versus no	1.43	1.06 to 1.93	<0.0179
Age (years)	Continuous	1.02	1.01 to 1.03	<0.0073

HAQ DI, Health Assessment Questionnaire Disability Index.

Table 4 Observed adalimumab effectiveness at week 12

	DAS28*		HAQ DI (0–3)*		TJC (0–28)		SJC (0–28)		CRP (mg/l)	
Patient group	Absolute change	Percentage change	Absolute change	Percentage change	Absolute change	Percentage change	Absolute change	Percentage change	Absolute change	Percentage change
All patients (n = 6610)	−2.1 (1.4)	−35.4	−0.54 (0.61)	−34.0	−8.0	−73.3	−6.0	−72.7	−5.5	−44.4
Number of concomitant DMARDs										
No DMARDs (n = 1731)	−1.9 (1.4)	−29.7	−0.47 (0.63)	−27.2	−7.0	−66.7	−6.0	−66.7	−4.5	−31.4
⩾1 DMARD (n = 4879)	−2.2 (1.3)	−37.3	−0.56 (0.60)	−36.4	−8.0	−75.0	−6.0	−75.0	−5.7	−47.8
1 DMARD (n = 4004)	−2.2 (1.3)	−37.2	−0.56 (0.6)	−36.3	−8.0	−75.0	−6.0	−75.0	−5.5	−47.3
2 DMARDs (n = 769)	−2.3 (1.3)	−38.0	−0.56 (0.6)	−36.8	−8.0	−75.0	−6.0	−75.0	−7.0	−50.5
⩾3 DMARDs (n = 106)	−2.3 (1.3)	−39.6	−0.56 (0.57)	−35.2	−9.0	−80.0	−7.0	−75.0	−5.7	−50.7
1 exclusive concomitant DMARD										
MTX (n = 2794)	−2.3 (1.3)	−38.3	−0.58 (0.6)	−38.4	−8.0	−75.0	−6.0	−75.0	−5.4	−47.5
LEF (n = 842)	−2.0 (1.3)	−33.7	−0.49 (0.59)	−29.5	−8.0	−75.0	−6.0	−69.2	−5.4	−44.6
AM (n = 148)	−2.4 (1.4)	−37.9	−0.72 (0.63)	−46.0	−9.0	−75.0	−7.0	−79.2	−8.1	−52.3
SSZ (n = 133)	−2.1 (1.3)	−34.2	−0.52 (0.62)	−29.6	−7.0	−66.7	−6.0	−66.7	−8.9	−54.2
1 other DMARD† (n = 84)	−2.2 (1.2)	−35.1	−0.55 (0.55)	−27.1	−8.0	−72.1	−7.0	−68.4	−9.7	−49.2
DMARD combinations										
MTX+LEF (n = 180)	−2.2 (1.3)	−36.4	−0.54 (0.58)	−36.3	−9.0	−76.9	−7.0	−78.9	−6.0	−46.2
MTX+AM (n = 269)	−2.4 (1.3)	−39.2	−0.63 (0.66)	−41.3	−8.0	−76.3	−6.0	−76.4	−4.7	−51.4
MTX+SSZ (n = 182)	−2.4 (1.3)	−39.8	−0.55 (0.52)	−38.8	−8.0	−76.4	−6.0	−75.0	−10.1	−56.7
MTX+SSZ+AM (n = 76)	−2.4 (1.3)	−40.7	−0.58 (0.59)	−37.6	−7.0	−80.0	−7.0	−75.8	−7.8	−55.2

AM, antimalarials; AZA, azathioprine; CRP, C-reactive protein; CsA, ciclosporin; DAS28, Disease Activity Score 28; DMARD, disease-modifying antirheumatic drug; HAQ DI, Health Assessment Questionnaire Disability Index; LEF, leflunomide; MTX, methotrexate; SJC, swollen joint count; SSZ, sulfasalazine; TJC, tender joint count. Absolute change is given as mean (SD) or median.
*All changes in DAS28 and HAQ DI scores were significantly improved compared with baseline values ($p \leqslant 0.001$).
†Of these 84 patients, 51% were receiving AZA, 27% were receiving parenteral gold, 17% were receiving CsA, and 5% were receiving penicillamine.

patients (previous drugs for <10% of patients are not shown). Of the 6610 patients, 2252 had no or one comorbid condition, and 4358 had two or more comorbid conditions.

Safety

Complete treatment period for all patients

This study represents 4210 patient-years (PYs) of adalimumab exposure. For the 72.4% of patients (4783/6610) who reported an AE, the three most common were RA-related events (9.7% (641/6610)), headache (4.8% (317/6610)) and nasopharyngitis (4.4% (293/6610)), and 9% were considered severe. Serious AEs (SAEs) occurred in 13% (882/6610) of patients (equivalent to 28.4 SAEs/100 PYs) (table 2). The three most commonly reported SAEs were RA-related events (2.0% (135/6610)), pyrexia (0.4% (25/6610)) and osteoarthritis (0.3% (20/66100).

Serious infections were reported for 202 of 6610 patients. Independent predictors for serious infection were pulmonary disease, male sex, higher HAQ DI score, cardiac disease, and increased age (table 3). Serious opportunistic infections (not including TB) occurred in <0.1% (6/6610) of patients and were caused by *Candida* (n = 1), cytomegalovirus (n = 3), *Listeria monocytogenes* (n = 1) and *Toxoplasma gondii* (n = 1).

Of the 6610 patients, 12.6% (832) had a positive Mantoux test result, and 3% (196) had a chest radiograph indicative of previous TB infection. Preventive treatment for latent TB infection was initiated in 835 patients (12.6%). Overall, 21 patients (mean age 60 years) were reported to have developed active TB (0.5/100 PYs); the diagnosis was confirmed by culture in 12 (57%) patients, was based on tissue staining of acid-fast bacilli in four patients, and was not confirmed in five patients. Of these 21 patients, eight had been screened with a Mantoux test that resulted in skin induration ⩾5 mm in diameter. However, only four of these eight patients had standard treatment for latent TB initiated (isoniazid 300 mg daily); treatment with isoniazid for one patient was stopped after 6 months, consistent with the national guideline. Isoniazid prophylaxis was not initiated in the other four patients because the threshold for latent TB treatment based on Mantoux testing was defined as skin induration ⩾10 mm in diameter by national guidelines, the patient had been immunised with the bacille Calmette-Guérin vaccine, or the patient had been recently treated with isoniazid for 11 months. The median interval from the first adalimumab injection to diagnosis of TB was 6 months (range 1–14). Eleven patients had extrapulmonary TB. The death of a woman aged 86 years who refused tuberculostatic treatment because of major gastrointestinal intolerance was attributed to TB.

Demyelinating disorders (all SAEs) occurred in 0.06% (4/6610) of patients as follows: multiple sclerosis (n = 1) and central demyelination (n = 1) (each confirmed by cerebral MRI), and Guillain-Barré syndrome (peripheral demyelination) (n = 2). Systemic lupus erythematosus based on an investigator's report was reported as an SAE for two of 6610 patients (0.03%).

Of 18 patients with congestive heart failure reported as an SAE (0.3%), 13 had pre-existing cardiovascular disorders (excluding peripheral vascular diseases).

The haematological AE rate was similar in patients receiving adalimumab with and without DMARDs (1.3% and 1.4%, respectively), whereas AEs of anaemia were more often considered serious for patients receiving adalimumab alone. Most haematological SAEs reported were unspecified or microcytic anaemia. Bone marrow toxicity and pancytopenia were reported in one patient each, both receiving concomitant DMARDs.

Forty three of 6610 patients had neoplasms that were counted as malignancies (the definition of neoplasms included those with no explicit benign character). For the SIR calculation, basal cell carcinoma and carcinoma in situ were excluded in accordance with the SEER algorithm. The total number of malignancies (32) was lower than expected (44.8), resulting in an SIR of 0.71 (95% CI 0.49 to 1.01) for malignancies in adalimumab-treated patients. The SIR for lymphomas was 1.09 (95% CI 0.12 to 3.95) based on the number of lymphomas observed (2) compared with the number expected (1.83).

The standardised mortality ratio was 1.07 (95% CI 0.75 to 1.49), with 35 deaths observed compared with 32.6 deaths expected in the general population.

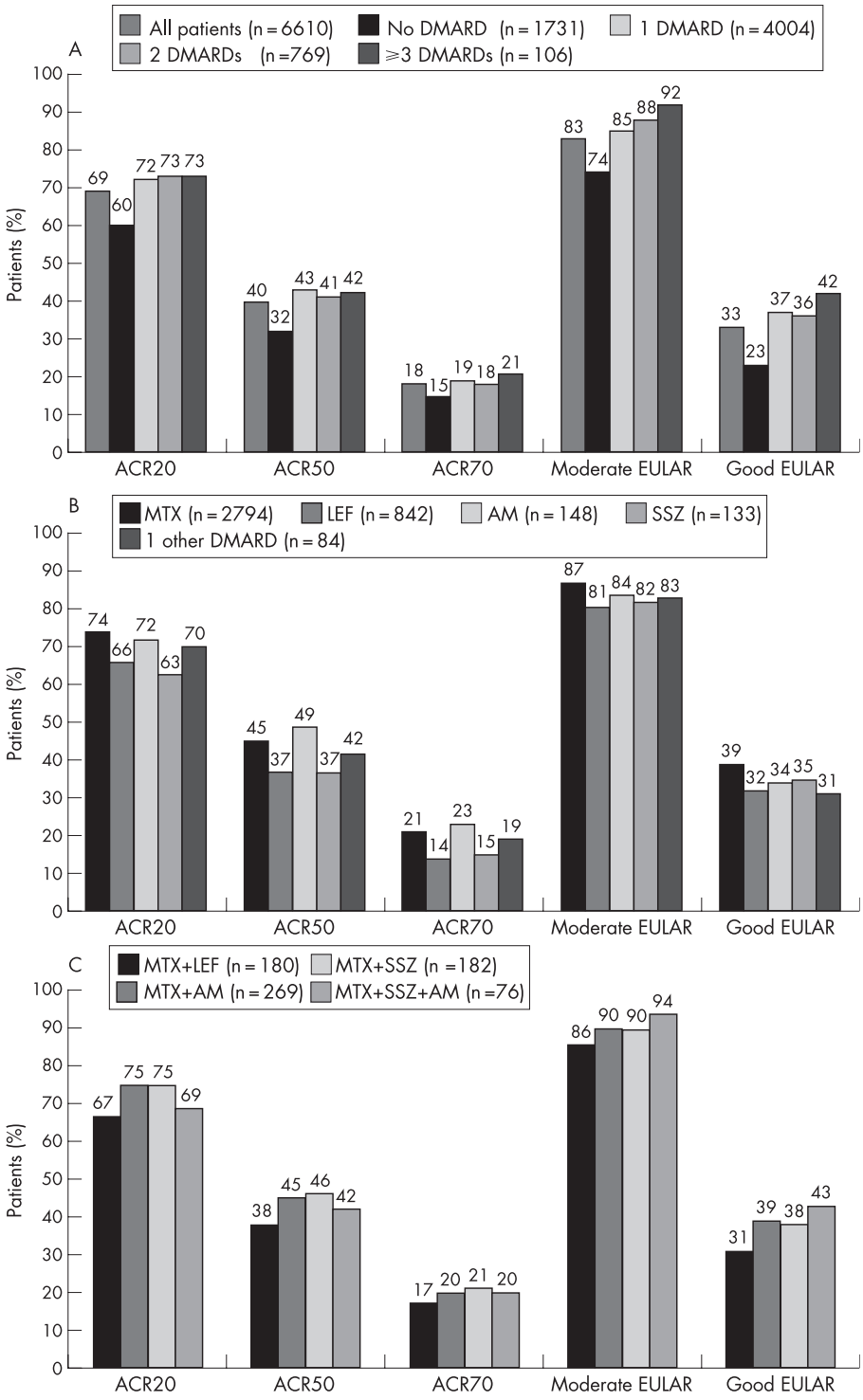

Figure 1 American College of Rheumatology 20% (ACR20), 50% (ACR50), and 70% (ACR70) improvement and European League Against Rheumatism (EULAR) responses to adalimumab treatment for all patients and by concomitant disease-modifying antirheumatic drug (DMARD) subgroup at week 12. The values above the bars are the percentages of patients achieving the response criterion. All values are observed. (A) Responses by number of concomitant DMARDs; (B) responses by exclusive concomitant DMARD; (C) responses by combinations of concomitant DMARDs. AM, antimalarials; LEF, leflunomide; MTX, methotrexate; SSZ, sulfasalazine.

Safety up to week 12

Monotherapy or various numbers of concomitant DMARDs

Of the 4879 patients who received adalimumab and at least one concomitant DMARD, 260 (5.3%) reported an SAE. Of the 1731 patients receiving no concomitant DMARDs, 126 (7.3%) reported an SAE. RA-related events were the most commonly reported SAE in patients receiving concomitant DMARD therapy (2.5/100 PYs) or adalimumab monotherapy (6/100 PYs). SAEs were reported less often for patients receiving adalimumab in combination with DMARDs (only one DMARD (5.5%), two DMARDs (4.4%), or at least three DMARDs (3.8%)) compared with patients receiving no concomitant DMARDs (7.3%).

Single concomitant DMARDs

The SAE rates for patients receiving adalimumab and only one concomitant DMARD were 4.1% for AM, 4.6% for MTX, 8.2% for LEF and 9.0% for SSZ. The serious infection rate was low in patients treated with a combination of adalimumab and MTX (1.1%), LEF (1.9%), AM (2.0%) or SSZ (2.3%), and was similar to the rate in patients receiving adalimumab alone (1.7%).

Cutaneous and subcutaneous AEs were reported in 17.3% of patients treated with adalimumab and LEF; of these, 0.8% were SAEs. No SAEs of the skin were documented for patients receiving concomitant AM or SSZ; SAEs of the skin were reported for 0.1% of patients treated with adalimumab and MTX.

Combinations of MTX and other concomitant DMARDs

The SAE rate in patients receiving adalimumab and MTX plus LEF, SSZ or AM was lower than in the groups receiving adalimumab and only LEF, SSZ or AM respectively. The percentages of patients with serious infection were 0.0% for MTX+SSZ, 1.1% for MTX+AM, 2.2% for MTX+LEF and 2.6% for MTX+SSZ+AM. Of 76 patients receiving adalimumab in addition to MTX+SSZ+AM, four (5.3%) experienced an SAE.

AZA, gold, CsA

Adalimumab was added to AZA alone or in combination with other DMARDs in 63 patients; two (3.2%) experienced an SAE. Two of 53 patients treated with adalimumab and parenteral gold (with or without other DMARDs) experienced an SAE. No infectious or cutaneous SAEs occurred during combination therapy with parenteral gold and adalimumab. Of the 25 patients who received CsA (alone or in combination with other DMARDs) in addition to adalimumab, two (8%) had an SAE. No change in the safety profile occurred when adalimumab was combined with AZA, parenteral gold, or CsA.

Effectiveness

The mean absolute and percentage changes in commonly used disease activity measures showed significant ($p \leqslant 0.001$) and clinically relevant improvements from baseline to week 12 for all patients and all concomitant DMARD subgroups (table 4). Overall ACR and EULAR responses are shown in fig 1. At week 12, 25% of all patients had a HAQ DI <0.5, and 20% had a DAS28 <2.6, which corresponds to fulfilment of the preliminary American Rheumatology Association criteria for clinical remission in RA.[24]

Concomitant DMARD subgroups

In the unadjusted univariate analyses, more patients receiving adalimumab and concomitant DMARDs (regardless of type or number of DMARDs) achieved ACR and EULAR responses and experienced more improvement in most measures of effectiveness than patients receiving adalimumab alone (fig 1 and table 4). More patients receiving adalimumab and either MTX or AM achieved ACR and EULAR responses and experienced greater reductions in disease activity and disability than patients receiving adalimumab and either SSZ or LEF (fig 1B and table 4).

This pattern of effectiveness among the different DMARDs was sustained after adjustment for baseline differences among the patient subgroups. Compared with the reference combination of adalimumab and MTX, the likelihood of achieving key effectiveness parameters was most similar (ie, ORs closest to 1.0) when adalimumab was added to AM or to the combination of MTX plus another DMARD (table 5).

DISCUSSION

This study is the largest prospective clinical evaluation of a TNF antagonist for the treatment of RA. The safety profile of adalimumab observed in this study was consistent with that previously reported for adalimumab, etanercept and infliximab.[1 3 25–27] The range of DMARDs used concomitantly with adalimumab in ReAct reflected standard treatment for patients with long-standing severe RA.[28–30] No clinically important differences in the safety profile of adalimumab according to the number or type of concomitant DMARDs were evident. Notably, the rate of AEs did not increase as the number and variety of concomitant DMARDs increased in ReAct, a finding

Table 5 Odds ratios for achieving a response at week 12 to adalimumab and various concomitant DMARDs compared with achieving a response to adalimumab and MTX alone after adjustment for baseline differences between groups

Concomitant DMARD group	Measurement of response					
	ACR20	ACR50	ACR70	Moderate EULAR	Good EULAR	DAS28 <2.6
No DMARDs	0.52 (0.45 to 0.60), <0.0001	0.61 (0.53 to 0.70), <0.0001	0.74 (0.62 to 0.87), 0.0004	0.45 (0.38 to 0.53), <0.0001	0.53 (0.46 to 0.62), <0.0001	0.59 (0.49 to 0.71), <0.0001
LEF	0.69 (0.58 to 0.82), <0.0001	0.72 (0.61 to 0.86), 0.0002	0.67 (0.54 to 0.84), 0.0006	0.68 (0.54 to 0.84), 0.0004	0.77 (0.64 to 0.93), 0.0058	0.75 (0.6 to 0.93), 0.0103
SSZ	0.61 (0.41 to 0.89), 0.0112	0.76 (0.52 to 1.11), 0.1555	0.76 (0.46 to 1.26), 0.2817	0.72 (0.44 to 1.16), 0.1756	0.95 (0.63 to 1.43), 0.8142	1.51 (0.97 to 2.36), 0.0694
AM	0.86 (0.58 to 1.26), 0.4292	1.14 (0.81 to 1.63), 0.4503	1.11 (0.73 to 1.68), 0.6397	0.81 (0.51 to 1.30), 0.3859	0.99 (0.67 to 1.44), 0.9420	1.03 (0.65 to 1.62), 0.9107
1 other DMARD*	0.82 (0.49 to 1.37), 0.4515	0.92 (0.57 to 1.48), 0.7280	1.08 (0.61 to 1.94), 0.7871	0.79 (0.42 to 1.46), 0.4446	0.97 (0.57 to 1.65), 0.9157	0.93 (0.48 to 1.81), 0.8365
MTX+LEF	0.67 (0.48 to 0.95), 0.0233	0.70 (0.50 to 0.97), 0.0307	0.72 (0.47 to 1.11), 0.1387	0.92 (0.59 to 1.45), 0.7183	0.72 (0.50 to 1.02), 0.0673	0.82 (0.53 to 1.25), 0.3491
MTX+AM	1.01 (0.74 to 1.38), 0.9465	0.94 (0.72 to 1.23), 0.6590	0.89 (0.64 to 1.24), 0.4860	1.33 (0.87 to 2.03), 0.1922	0.99 (0.75 to 1.32), 0.9493	0.97 (0.69 to 1.34), 0.8310
MTX+SSZ	1.01 (0.71 to 1.45), 0.9452	1.0 (0.73 to 1.36), 0.9822	0.99 (0.67 to 1.44), 0.9438	1.36 (0.82 to 2.24), 0.2366	0.94 (0.67 to 1.32), 0.7336	1.01 (0.68 to 1.48), 0.9729
MTX+SSZ+AM	0.86 (0.51 to 1.45), 0.5708	0.97 (0.59 to 1.57), 0.8849	1.11 (0.62 to 2.0), 0.7208	2.89 (1.04 to 8.01), 0.0411	1.24 (0.74 to 2.09), 0.4180	1.61 (0.91 to 2.84), 0.1006

American College of Rheumatology 20% (ACR20), 50% (ACR50), and 70% (ACR70) improvement; AM, antimalarials; CsA, ciclosporin; DAS28, Disease Activity Score 28; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; LEF, leflunomide; MTX, methotrexate; SSZ, sulfasalazine.
Values are OR (95% CI), p value. ORs were calculated using the combination of adalimumab and MTX as the reference (OR = 1.0).
*1 DMARD refers to a single concomitant DMARD other than MTX, LEF, SSZ, or AM.

that is consistent with use of multiple DMARDs in other studies.[31 32] The combinations of adalimumab and LEF or SSZ were associated with higher rates of SAEs compared with patients receiving adalimumab and MTX or AM.

Rheumatoid arthritis and age are both known risk factors for infection.[19 33] The serious infection rate of 5.5/100 PYs is similar to reports of patients with RA receiving either infliximab or etanercept in the German and British biologics registries[20 34]; these rates were somewhat higher than those seen in patients treated with conventional DMARDs in these registries. The identified predictors for a serious infection in this study were increased age, male sex, comorbid pulmonary and cardiovascular conditions, and a higher baseline HAQ DI score.

All patients were carefully screened for latent TB before enrolment. In total, 835 patients (12.6%) received treatment for latent TB in accordance with national guidelines. Overall, published literature indicates that the rate of active TB has decreased since the initiation of routine screening for latent TB in patients receiving TNF antagonists.[27 35] In the present study, the rate of TB (0.5/100 PYs) remains higher than expected in the general population. However, the underlying risk of TB in patients with RA seems to exceed that of the background population.[35 36]

The SIRs of 0.71 for malignancies and 1.09 for lymphoma in this study are consistent with rates observed in patients with RA (SIR of 0.98−1.1 for malignancies overall and SIR of 1.0−11.5 for lymphoma).[13 37–39] A meta-analysis of pooled AE data from randomised, controlled trials suggested an OR of 3.3 (95% CI 1.2 to 9.1) for malignancies.[40] Calculation of SIRs based on population-based incidence data and determination of ORs based on meta-analytical methodology both have limitations. Analysis of a clinical trial safety database of 10 050 adalimumab-treated patients with RA reported an SIR of 1.06 for malignancies overall and an SIR of 3.19 for lymphoma.[27] Notably, there is a strong association between inflammatory activity and lymphoma in patients with RA.[41] The standardised mortality ratio of 1.07 (95% CI 0.75 to 1.49) was slightly lower than the expected range for patients with RA.[42]

Adalimumab provided substantial improvement in multiple measures of effectiveness in patients with long-standing active RA despite extensive standard treatment. Randomised, controlled trials have shown that significantly more patients experience a reduction of disease activity when treated with MTX and a TNF antagonist versus a TNF antagonist alone.[1–3] After adjustment for differences in baseline characteristics in this study, patients receiving adalimumab and an AM had a similar therapeutic response to the patients receiving adalimumab and MTX. Concomitant treatment with adalimumab and LEF was found to be slightly less effective than concomitant treatment with adalimumab and MTX, AM or SSZ but more effective than adalimumab alone after adjustment for differences in baseline characteristics between subgroups.

Although a placebo-controlled trial is necessary to prove the efficacy of a drug, an open-label study conducted in a large cohort of patients in multiple countries and a variety of clinical practice sites should provide reassurance about the safety and effectiveness of adalimumab in typical practice. The ACR20 response rates in ReAct were within the range reported in randomised, double-blind studies of adalimumab.[1 25 43 44] The duration of RA and baseline disease activity of participants reflect the RA population typically treated with TNF antagonists and are consistent with most national guidelines for this treatment. By comparison with national biologic registers, which observe treatment outcomes associated with a variety of biologics for several years, this was an industry-sponsored clinical study conducted in 12 countries with careful site monitoring for a limited treatment period.

CONCLUSIONS

Adalimumab alone or in combination with standard DMARDs appeared to be well tolerated and effective in 6610 patients with active RA despite numerous previous antirheumatic treatments and various comorbid medical disorders. There were no unexpected safety concerns with the addition of adalimumab to existing DMARD regimens.

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