

# Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice

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**Objective.** To evaluate the effectiveness and safety of adalimumab in patients with rheumatoid arthritis (RA) who previously discontinued tumour necrosis factor (TNF) antagonists for any reason in clinical practice.

**Methods.** ReAct (Research in Active Rheumatoid Arthritis) was a large, open-label trial that enrolled adults with active RA who had previously been treated with traditional disease-modifying anti-rheumatic drugs or biological response modifiers. Patients self-administered adalimumab 40 mg subcutaneously every other week for 12 weeks and were allowed to enter an optional long-term extension phase. Measures of adalimumab effectiveness included American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) response criteria, Disease Activity Score 28 (DAS28) and the Health Assessment Questionnaire Disability Index (HAQ DI).

**Results.** Of 6610 patients, 899 had a history of etanercept and/or infliximab therapy; these patients experienced substantial clinical benefit from adalimumab treatment. At week 12, 60% of patients had an ACR20 and 33% had an ACR50 response; 76% had a moderate and 23% had a good EULAR response. In addition, 12% achieved a DAS28 <2.6, indicating clinical remission, and 13% achieved a HAQ DI score <0.5. The allergic adverse event rate, regardless of relationship to adalimumab, was 6.5/100-patient-years (PYs) in previously TNF-antagonist-exposed patients and 4.3/100-PYs in TNF-antagonist-naïve patients. A multiple regression analysis indicated no statistically significantly increased risk of serious infections in patients who received prior TNF antagonists compared with TNF-antagonist-naïve patients.

**Conclusion.** In typical clinical practice, adalimumab was effective and well-tolerated in patients with RA previously treated with etanercept and/or infliximab.

**KEY WORDS:** Adalimumab, Etanercept, Infliximab, TNF antagonist, Rheumatoid arthritis.

## Introduction

Biologic response modifiers that target tumour necrosis factor (TNF) inhibition have become established therapies for active rheumatoid arthritis (RA) in recent years. Sustained efficacy of adalimumab, etanercept and infliximab has been demonstrated, significantly improving symptoms and limiting progression of joint destruction and subsequent disability of patients with RA [1–3]. The therapeutic efficacy of all three TNF antagonists is postulated from their ability to bind soluble TNF and prevent its binding to the natural TNF receptor. TNF blockade in combination with methotrexate significantly reduces clinical disease activity and halts joint destruction in most patients with early or longstanding RA [4–7]. Even if disease activity is not substantially reduced, TNF blockade has been shown to reduce joint destruction, suggesting that inflammation and joint destruction can be disconnected and are independently controlled by TNF inhibition [8]. These effects have been attributed to the role of TNF in both synovitis and the activation and differentiation of osteoclasts, the mediators of bone destruction in RA [9].

Although TNF antagonists are an important advance in the therapy of RA, some patients with RA may be intolerant of

these agents or may not experience a clinically meaningful response [10]. A practical question faced by clinicians and patients is whether switching TNF blockers is likely to produce improved clinical response and tolerability. In fact, there are data indicating that switching among the three available TNF antagonists (adalimumab, etanercept and infliximab) is safe and effective, with few withdrawals because of intolerance or lack of efficacy [11–28]. New biological agents for the treatment of RA, such as rituximab and abatacept, also factor into the therapeutic decision faced by clinicians and patients. Because current data indicate that non-response to one TNF antagonist does not preclude a response to another, an additional TNF-antagonist trial may be warranted before moving on to another biological agent. There is a need for additional data to document the safety and effectiveness of switching among TNF antagonists in clinical practice to guide clinicians' choice of treatment after failure of anti-TNF therapy.

The ReAct (Research in Active Rheumatoid Arthritis) trial is the largest study of a TNF antagonist to assess the safety and effectiveness of adalimumab, with or without concomitant disease-modifying anti-rheumatic drugs (DMARDs), in routine clinical practice [29]. Of the 6610 patients who participated in ReAct, the current analysis evaluated the effectiveness of adalimumab in 899 patients who had previously been treated with etanercept and/or infliximab.

## Methods

This was an open-label, multicentre study conducted at 448 centres in 11 European countries and Australia in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent before any study procedure was completed.

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## Patients

Patients were  $\geq 18$  yrs of age and had a clinical diagnosis of RA, fulfilling the 1987 revised American College of Rheumatology (ACR) criteria [30] for  $\geq 3$  months, and a Disease Activity Score 28 (DAS28) [31]  $\geq 3.2$  despite standard anti-rheumatic treatment including at least one traditional DMARD. Patients previously or currently treated with alkylating agents were excluded from participation. Prior therapy with biologic response modifiers (e.g. anakinra, etanercept and infliximab) was allowed if treatment was discontinued at least 2 months before study entry. Information on the dosage regimen of each prior TNF antagonist, including duration of treatment and date of last dose, was collected at study entry. The investigator retrospectively completed a questionnaire requesting the reason for discontinuation of prior TNF-antagonist therapy [i.e. never achieved satisfactory response (no response), loss of initial response (loss of response), intolerance, other and unknown]. Further details of prior therapy were not obtained.

All patients were evaluated for latent tuberculosis infection (LTBI) using the Mantoux test. Unless national guidelines provided a different definition, investigators considered the test result positive for LTBI when the skin induration was  $\geq 5$  mm. Patients with LTBI were allowed to participate in ReAct if a documented history of prophylactic treatment was available or prophylactic treatment for LTBI in accordance with national guidelines was initiated before self-administering the first dose of adalimumab. Patients with a history of active tuberculosis, malignancies, currently active infections, a history or signs of demyelinating disorders and uncontrolled medical conditions were excluded from participation.

## Study design

Patients self-administered adalimumab 40 mg by subcutaneous injection every other week for 12 weeks with an option to enter an extension phase until adalimumab was approved and commercially available, provided that the study investigator determined that patients were benefiting from treatment. This open-label study was designed to reflect treatment of RA in typical clinical practice, and no placebo group was included for comparison. Adalimumab 40 mg was provided in pre-filled syringes (Abbott Laboratories, Abbott Park, IL). Patients were allowed to continue current anti-rheumatic therapy, including DMARDs or any combination of DMARDs, glucocorticoids (prednisone equivalent  $\leq 10$  mg/day) and non-steroidal anti-inflammatory drugs, provided that dosage regimens were stable until week 12.

The effectiveness of adalimumab was assessed at weeks 2, 6 and 12 and every 8 weeks in the extension phase using ACR20, ACR50, ACR70 [31] and European League Against Rheumatism (EULAR) response criteria [32]. Additional measures of effectiveness were the DAS28 (calculated using erythrocyte sedimentation rate and an evaluation of 28 joints) [33]; the Health Assessment Questionnaire Disability Index (HAQ DI) [34]; tender (0–28) and swollen (0–28) joint counts; C-reactive protein (CRP) concentration (mg/l); and the patient's assessment of pain and the physician's global assessment of disease activity (both assessed using a 0–100-mm visual analogue scale). Routine safety assessments included physical examinations, standard laboratory measures and reports of adverse events (AEs) throughout the entire treatment period for each patient.

## Statistical analyses

Descriptive analyses of safety and effectiveness were performed for all patients who received at least one adalimumab injection. Data were categorized in two major patient groups: (i) patients who were naive to TNF-antagonist treatment and (ii) patients who were treated with prior TNF antagonists (etanercept

and/or infliximab). For patients treated with a prior TNF antagonist, the following subgroups were defined for additional analyses of adalimumab effectiveness: exclusive use of etanercept or infliximab; use of both etanercept and infliximab; reason for discontinuation of any prior TNF antagonist (i.e. no response, loss of response, intolerance); reason for discontinuation of etanercept exclusively (i.e. no response, loss of response, intolerance); and reason for discontinuation of infliximab exclusively (i.e. no response, loss of response, intolerance). Patients who had discontinued a prior TNF antagonist because of no response or loss of response and intolerance were included in the analyses of both adalimumab effectiveness and safety. No patient was categorized as having discontinued a prior TNF antagonist because of both no response and loss of response. No response and loss of response, respectively, superseded all other reasons for discontinuation in the analyses of adalimumab effectiveness. Patients in the intolerance subgroup had discontinued a prior TNF antagonist exclusively because of intolerance. Patients who discontinued a prior TNF antagonist exclusively because of unknown or other reasons were not included in the analyses by reason for discontinuation.

Analyses of adalimumab effectiveness were based primarily on the week-12 observed values and secondarily on the last observation of each patient during the extension phase irrespective of time-point. The observed mean changes in DAS28, HAQ DI scores, tender and swollen joint counts, CRP concentration, patient's assessment of pain and physician's global assessment of disease activity from baseline to week 12 and to the last observation, respectively, were analysed by paired *t*-test. Additional measures of adalimumab effectiveness at week 12 were a DAS28  $< 2.6$  as an indicator of clinical remission [35] and a HAQ DI score  $< 0.5$ . Week 12 was chosen as the time-point for analysis of adalimumab effectiveness in accordance with the international consensus statements on biologic agents that require significant improvement within a 12-week treatment period [36, 37]. Also, placebo-controlled, Phase III trials demonstrated that the vast majority of patients who respond to adalimumab do so by 12 weeks [38–41]. AEs were summarized for all patients who previously failed TNF-antagonist treatment and by the subgroups described earlier.

Kaplan–Meier survival estimates were used to evaluate the time to adalimumab treatment discontinuation for subgroups by reason for discontinuation of prior TNF-antagonist treatment. Patients who withdrew from the study and discontinued adalimumab treatment were categorized as discontinuing adalimumab; patients who withdrew from the study because of study completion as planned or who withdrew from the study but continued to receive commercially available adalimumab were categorized as survivors. Three survival curves were generated based on the reason for discontinuation of prior etanercept and/or infliximab treatment; one each for patients who discontinued exclusively because of no response, loss of response, or intolerance. For each curve, the rate of adalimumab continuation was calculated as the number of patients who continued adalimumab at a given time-point divided by the number of all patients who started adalimumab treatment.

To evaluate the possible impact of previous treatment with TNF antagonists on the occurrence of serious infections, a multiple Cox regression analysis was performed for the safety endpoint of serious infection. If a patient did not have a serious infection, his/her observation time in the study was included in the analysis. If a patient experienced a serious infection, time to the first serious infection was included in the analysis. The following prognostic factors were specified a priori and included in the model selection process: age (yrs); sex; medical history of diabetes mellitus, cardiac or pulmonary disease; tobacco use (ever); duration of RA (yrs); number of previous DMARDs; concomitant corticosteroid use; leflunomide use; baseline DAS28; baseline CRP concentration (mg/l); baseline HAQ DI score; rheumatoid

factor (RF) (+/-); leucopenia (<3.5/nl); and history of TNF-antagonist use (yes/no). Only factors that were significant at the  $P < 0.1$  level in the univariate analysis were entered into the backward selection process of the multiple Cox regression.

## Results

### Baseline characteristics

Of the 6610 patients enrolled in ReAct, 5711 patients had never been treated with a TNF antagonist and 899 patients had received prior treatment with etanercept and/or infliximab. The percentage of females (~80%), mean age (range 52–54 yrs), mean duration of RA (11–12 yrs) and RF positivity were similar in both groups (Table 1). Compared with the TNF-antagonist-naïve group, patients treated with a prior TNF antagonist had received more prior DMARDs (even if biologics were not included); had somewhat higher disease activity as indicated by the mean baseline DAS28 (6.3 vs 6.0 for the TNF-antagonist-naïve group); and had more tender and swollen joints. In addition, patients previously treated with TNF antagonists were more disabled at baseline, as indicated by higher mean baseline HAQ DI scores (1.85 vs 1.60 for the TNF-antagonist-naïve patients). More patients in the prior TNF-antagonist treatment group (31%) were receiving adalimumab monotherapy in the current study compared with TNF-antagonist-naïve patients (25%).

Overall, 591 patients were previously treated with infliximab only, 188 patients were previously treated with etanercept only and 120 patients had been treated with both TNF antagonists. Questionnaires providing the details of prior TNF-antagonist treatment were completed for 870 patients. Prior TNF antagonists had been discontinued exclusively because of each of the following reasons: no response in 195 patients, loss of response in 327 patients and intolerance in 190 patients. Of 507 previously infliximab-treated patients with a documented reason for discontinuation, infliximab was discontinued as follows: no response (22% of patients), loss of response (51%) and intolerance (27%). Of 151 previously etanercept-treated patients with a documented reason for discontinuation, etanercept was

discontinued as follows: no response (42% of patients), loss of response (32%) and intolerance (26%).

At baseline, patients previously treated with etanercept had a longer duration of RA and higher disease activity compared with patients previously treated with infliximab. In addition, 50% of previously etanercept-treated patients were receiving no DMARDs at baseline compared with 25% of previously infliximab-treated patients. Baseline characteristics for the subgroups by reason for discontinuation of prior TNF-antagonist therapy were similar. Patients who discontinued their previous anti-TNF treatment because of insufficient efficacy and patients with a treatment history of both TNF antagonists had notably high baseline HAQ DI scores (1.9 for both groups). Prior TNF-antagonist treatment duration and intervals between the last dose of a prior TNF antagonist and the first dose of adalimumab are summarized for all subgroups in Table 1. In a subset of 81 patients who had their last infliximab infusion within 12 weeks before the first adalimumab injection, the mean/median baseline DAS28 was 6.4/6.6.

### Patient disposition and exposure to adalimumab

At week 12, 90% of the 899 patients previously treated with a TNF antagonist and 93% of the 5711 TNF-antagonist-naïve patients remained in the study (Table 2). Overall, the mean exposure to adalimumab was 30 weeks (28 median) in patients previously treated with a TNF antagonist and 34 weeks (32 median) in TNF-antagonist-naïve patients.

### Effectiveness

**Prior TNF-antagonist treatment.** After 12 weeks of open-label treatment with adalimumab, statistically significant and clinically important improvements from baseline occurred in all measures of RA activity in the prior TNF-antagonist patients and in the TNF-antagonist-naïve patients. An ACR20 response was achieved by 60% of patients who had previously been treated with a TNF antagonist and 70% of TNF-antagonist-naïve patients (Table 3). A similar pattern of ACR50, ACR70 and EULAR responses was observed for these two groups of patients. Based on the last observation values during the extension phase of

TABLE 1. Baseline demographic and clinical characteristics

Characteristic	No Prior TNF Antagonist <sup>a</sup> (n=5711)	Prior TNF Antagonist <sup>a</sup> (n=899)	Prior IFX Only (n=591)	Prior ETN Only (n=188)	Prior ETN and IFX (n=120)	Reason for Discontinuation of Prior TNF Antagonist <sup>b</sup>	
						Effectiveness (n=544)	Safety Only (n=190)
Age (yrs)	54 ± 13	53 ± 13	53 ± 13	54 ± 13	52 ± 11	54 ± 12	53 ± 13
Female, (%)	81	81	80	80	86	82	78
Rheumatoid factor positive, (%)	73	72	72	71	75	72	71
Disease duration, (yrs)	11 ± 9	12 ± 8	12 ± 8	13 ± 9	12 ± 7	12 ± 8	12 ± 8
Number of previous DMARDs	2.7 ± 1.6	5.0 ± 1.9	4.6 ± 1.6	5.2 ± 1.9	7.1 ± 1.9	5.1 ± 1.9	4.9 ± 2.0
Disease Activity Score 28	6.0 ± 1.1	6.3 ± 1.1	6.2 ± 1.1	6.5 ± 1.2	6.6 ± 1.1	6.4 ± 1.1	6.4 ± 1.1
HAQ DI score (0–3)	1.60 ± 0.68	1.85 ± 0.66	1.83 ± 0.67	1.89 ± 0.68	1.93 ± 0.59	1.91 ± 0.63	1.82 ± 0.69
Tender joint count (0–28 joints)	13 ± 7	15 ± 7	14 ± 7	16 ± 7	16 ± 7	15 ± 7	16 ± 7
Swollen joint count (0–28 joints)	10 ± 6	11 ± 6	11 ± 6	12 ± 6	13 ± 6	12 ± 6	12 ± 6
Patient's global assessment of pain (0–100-mm visual analogue scale)	64 ± 22	70 ± 20	68 ± 21	73 ± 19	73 ± 18	70 ± 20	69 ± 21
Physician's global assessment of disease activity (0–100-mm visual analogue scale)	59 ± 17	65 ± 17	64 ± 17	67 ± 17	69 ± 17	67 ± 16	64 ± 17
No concomitant DMARDs, (%)	25	31	25	50	32	32	33
Concomitant steroid use, (%)	70	77	75	78	83	77	77
Time from last prior TNF-antagonist dose to first adalimumab dose (weeks), mean/median	NA	36/17	35/17	42/22	32/17	33/15	40/23
Prior TNF-antagonist treatment duration (weeks), mean/median	NA	53/41	51/41	48/30	69/55	57/45	38/29

Values are observed mean ± s.d., unless otherwise noted.

<sup>a</sup>Prior TNF antagonist includes etanercept and/or infliximab.

<sup>b</sup>Effectiveness reason includes patients who experienced no response or loss of response to prior TNF antagonist irrespective of intolerance or other reasons. Safety reason refers to intolerance as the exclusive reason for discontinuation of a prior TNF antagonist.

DMARD = disease-modifying anti-rheumatic drug; ETN = etanercept; HAQ DI = Health Assessment Questionnaire Disability Index; IFX = infliximab; NA = not applicable; TNF = tumour necrosis factor.

TABLE 2. Withdrawal rates by subgroups

Withdrawals <sup>a</sup>	No prior TNF antagonist <sup>b</sup> (n=5711)	Prior TNF antagonist <sup>b</sup> (n=899)	Prior IFX Only (n=591)	Prior ETN Only (n=188)	Reason for discontinuation of prior ETN or IFX only <sup>c</sup>					
					No Response		Loss of Response		Intolerance	
					IFX (n=110)	ETN (n=63)	IFX (n=258)	ETN (n=48)	IFX (n=139)	ETN (n=40)
Withdrawals up to Week 12, n (%)	381 (7)	89 (10)	50 (9)	20 (11)	7 (6)	7 (11)	20 (8)	4 (8)	13 (9)	5 (13)
Adverse event, n (%)	234 (4)	50 (6)	33 (6)	10 (5)	5 (5)	3 (5)	14 (5)	2 (4)	10 (7)	2 (5)
Lack of effectiveness, n (%)	68 (1)	26 (3)	12 (2)	5 (3)	2 (2)	3 (5)	4 (2)	1 (2)	3 (2)	0
Withdrawals during complete treatment period, n (%)	1147 (20)	230 (26)	144 (24)	50 (27)	33 (30)	15 (24)	49 (19)	15 (31)	40 (29)	12 (30)
Adverse event, n (%)	569 (10)	113 (13)	78 (13)	20 (11)	18 (16)	6 (10)	27 (11)	4 (8)	24 (17)	5 (13)
Lack of effectiveness, n (%)	355 (6)	95 (11)	56 (10)	21 (11)	11 (10)	8 (13)	23 (9)	6 (13)	12 (9)	4 (10)

<sup>a</sup>Multiple reasons for study withdrawal were allowed. Additional reasons for withdrawal not reported in the table were withdrawal of consent, protocol violation and other causes.

<sup>b</sup>Prior TNF antagonists include etanercept and/or infliximab.

<sup>c</sup>Reasons for discontinuation of prior TNF-antagonist treatment are summarized for those patients who received either etanercept or infliximab exclusively. Those patients who had discontinued prior ETN or IFX treatment for both an effectiveness and safety reason were assigned to the corresponding effectiveness subgroup (no response or loss of response). The intolerance subgroup consists of patients who had discontinued prior ETN or IFX treatment exclusively because of intolerance.

ETN, etanercept; IFX, infliximab; TNF, tumour necrosis factor.

TABLE 3. Observed adalimumab effectiveness at week 12

	No Prior TNF Antagonist <sup>a</sup> (n=5711)	Prior TNF Antagonist <sup>a</sup> (n=899)	Prior IFX Only (n=591)	Prior ETN Only (n=188)	Prior ETN and IFX (n=120)	Reason for Discontinuation of Prior ETN or IFX Only <sup>b</sup>					
						No response		Loss of response		Intolerance	
						IFX (n=110)	ETN (n=63)	IFX (n=258)	ETN (n=48)	IFX (n=139)	ETN (n=40)
ACR20 response, (%)	70	60	64	57	46	59	41	67	67	67	67
ACR50 response, (%)	41	33	34	34	29	25	26	37	34	37	42
ACR70 response, (%)	19	13	13	13	11	7	11	13	14	16	19
Moderate EULAR response, (%)	84	76	78	79	62	73	75	79	81	83	89
Good EULAR response, (%)	35	23	26	21	11	18	20	23	19	31	20
DAS28											
Absolute change <sup>c</sup>	-2.2 ± 1.3	-1.9 ± 1.4	-2.0 ± 1.4	-2.0 ± 1.4	-1.5 ± 1.4	-1.8 ± 1.4	-2.0 ± 1.6	-2.0 ± 1.4	-2.2 ± 1.4	-2.3 ± 1.3	-2.3 ± 1.2
Percent change	-36	-31	-32	-31	-23	-28	-30	-31	-33	-36	-34
HAQ DI score (0-3)											
Absolute change <sup>c</sup>	-0.55 ± 0.61	-0.48 ± 0.60	-0.51 ± 0.60	-0.43 ± 0.61	-0.40 ± 0.59	-0.51 ± 0.54	-0.33 ± 0.54	-0.52 ± 0.61	-0.46 ± 0.67	-0.55 ± 0.64	-0.54 ± 0.66
Percent change	-35	-25	-29	-16	-22	-26	-15	-29	-20	-32	-4
Tender joint count (0-28 joints)											
Absolute change <sup>c</sup>	-9 ± 7	-8 ± 7	-8 ± 7	-9 ± 7	-8 ± 8	-7 ± 7	-10 ± 7	-8 ± 7	-10 ± 8	-9 ± 7	-11 ± 7
Percent change	-62	-55	-56	-56	-46	-49	-54	-56	-57	-60	-60
Swollen joint count (0-28 joints)											
Absolute change <sup>c</sup>	-7 ± 6	-7 ± 6	-7 ± 5	-8 ± 6	-6 ± 6	-7 ± 6	-7 ± 6	-7 ± 5	-8 ± 6	-8 ± 5	-8 ± 6
Percent change	-63	-58	-59	-61	-43	-52	-59	-63	-64	-65	-67
Patient's global assessment of pain (0-100-mm VAS)											
Absolute change <sup>c</sup>	-31 ± 28	-29 ± 28	-30 ± 28	-28 ± 28	-25 ± 30	-26 ± 28	-26 ± 26	-31 ± 28	-28 ± 33	-33 ± 26	-34 ± 25
Relative change	-43	-37	-38	-36	-32	-32	-32	-36	-33	-47	-44
Physician's global assessment of disease (0-100 mm VAS)											
Absolute change <sup>c</sup>	-34 ± 22	-32 ± 23	-33 ± 22	-33 ± 25	-30 ± 24	-33 ± 24	-31 ± 27	-34 ± 23	-31 ± 23	-34 ± 20	-41 ± 21
Relative change	-54	-49	-50	-47	-44	-46	-40	-51	-47	-54	-59
DAS28 < 2.6 (%)	21	12	14	13	4	9	15	12	12	18	9
HAQ DI < 0.5 (%)	27	13	13	11	11	9	5	13	11	17	17

Data are mean ± s.d. unless otherwise noted.

<sup>a</sup>Prior TNF antagonists include etanercept and/or infliximab.

<sup>b</sup>Reasons for discontinuation of prior TNF-antagonist treatment are summarized for those patients who received either etanercept or infliximab exclusively. Those patients who had discontinued prior ETN or IFX treatment for both an efficacy and safety reason were assigned to the corresponding effectiveness subgroup (no response or loss of response). The intolerance subgroup consists of patients who had discontinued prior ETN or IFX treatment strictly because of intolerance.

<sup>c</sup>P < 0.001 vs baseline based on paired t-test for all subgroups.

ACR, American College of Rheumatology; DAS28, Disease Activity Score based on 28-joint count; ETN, etanercept; EULAR, European League Against Rheumatism; HAQ DI, Health Assessment Questionnaire Disability Index; IFX, infliximab; VAS, visual analogue scale.



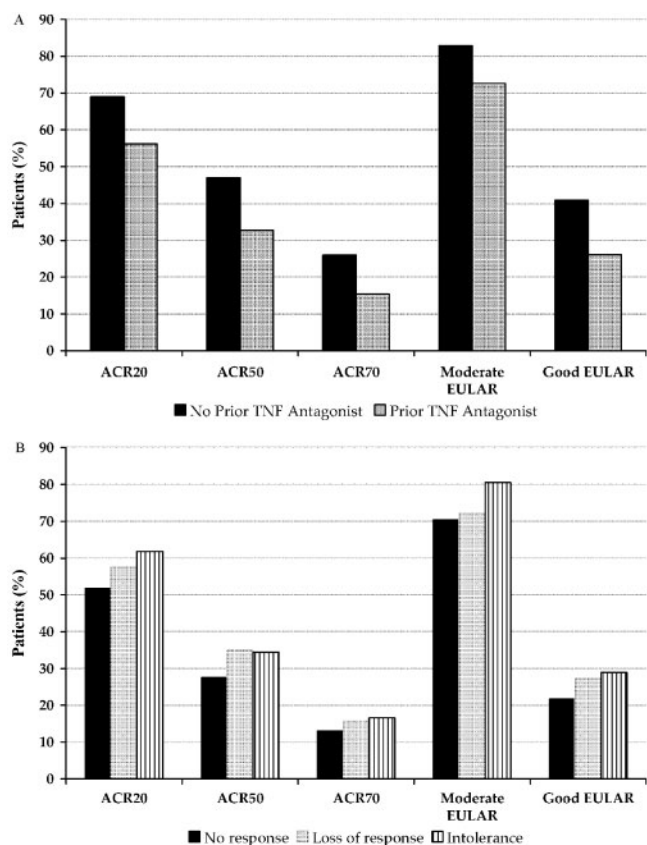


FIG. 1. American College of Rheumatology 20% (ACR20), 50% (ACR50) and 70% (ACR70) improvement and European League Against Rheumatism (EULAR) responses to adalimumab treatment. (A) Patients with no prior TNF-antagonist therapy ( $n=5711$ ) and patients who received prior TNF-antagonist therapy ( $n=899$ ). (B) Patients who had discontinued prior TNF-antagonist treatment because of no response ( $n=195$ ), loss of response ( $n=327$ ), or intolerance ( $n=190$ ). Values are last observations irrespective of time-point.

adalimumab treatment, the ACR50, ACR70 and good EULAR response rates increased for both groups after week 12 (Fig. 1A). The mean changes from baseline in DAS28, HAQ DI score, tender and swollen joint counts, patient's assessment of pain and physician's global assessment of disease activity were clinically and statistically significantly improved in both patients with and without a history of anti-TNF therapy (Table 3). At week 12, 27% of the 5711 TNF-antagonist-naïve patients achieved a HAQ DI score  $<0.5$ , and 21% of these patients had a DAS28  $<2.6$ . Of the 899 patients in the prior TNF-antagonist group (who had a higher mean baseline DAS28 and HAQ DI score), 13% had a HAQ DI score  $<0.5$  and 12% of these patients had a DAS28  $<2.6$  at week 12. At the last observation, 16% of these patients had achieved a HAQ DI score  $<0.5$  and 16% had a DAS28  $<2.6$ .

*Prior treatment with either infliximab or etanercept.* Subgroup analyses indicated that patients who had received prior treatment with either infliximab or etanercept exclusively achieved ACR and EULAR responses that were similar in magnitude to the responses achieved by the overall prior TNF-antagonist group; however, the percentage of patients who achieved an ACR20 response and a good EULAR response was lower in the etanercept-only group (Table 3). Improvement in DAS28, HAQ DI scores, joint counts, patient's assessment of pain and physician's global assessment of disease activity were clinically relevant and statistically significant ( $P < 0.001$ ) for both groups during adalimumab treatment (Table 3).

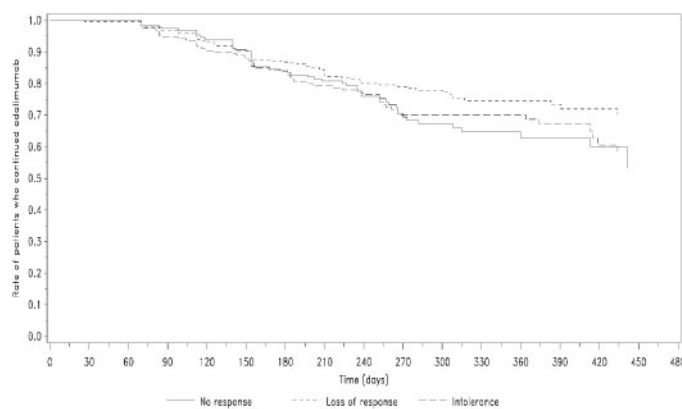


FIG. 2. Adalimumab treatment continuation as represented by Kaplan-Meier survival curves. Each curve represents the rate of adalimumab continuation by the specific reason for discontinuation of prior TNF-antagonist therapy (etanercept and/or infliximab). The three curves represent patients who discontinued prior etanercept and/or infliximab treatment exclusively because of 'no response' ( $n=195$ ); exclusively because of 'loss of response' ( $n=327$ ); or exclusively because of 'intolerance' ( $n=190$ ).

*Prior treatment with two TNF antagonists.* Of the 120 patients who had previously been treated with both etanercept and infliximab, 46% achieved an ACR20 response, 29% achieved an ACR50 response and 62% achieved at least a moderate EULAR response during adalimumab treatment. These patients also had marked improvements in DAS28, HAQ DI score, joint counts and other measures of effectiveness (Table 3). The treatment order of prior TNF antagonists had no impact on adalimumab effectiveness.

*Reason for discontinuation of prior TNF antagonist.* Adalimumab treatment led to clinically relevant improvement of disease activity irrespective of the reason for stopping a prior TNF antagonist. Of those 190 patients who had formerly discontinued etanercept and/or infliximab because of intolerance, 39% achieved an ACR50 response at week 12. The ACR50 response rate was 36% in the 327 patients who had stopped etanercept and/or infliximab because of loss of response and 26% in the 195 patients who had no response to etanercept and/or infliximab. The ACR and EULAR response rates at the last observation stratified by reason for discontinuation of prior anti-TNF therapy were highest in patients who had discontinued their prior TNF antagonist because of intolerance (Fig. 1B). However, for patients who had experienced a loss of response to prior TNF antagonists, there was a trend toward a higher probability of these patients continuing adalimumab treatment compared with patients who experienced no response or intolerance to prior TNF antagonists (Fig. 2). Of note, the mean duration of adalimumab exposure in the current study did not surpass the previous mean duration of prior TNF-antagonist exposure.

For patients who lost response to or were intolerant of prior infliximab or etanercept treatment, the ACR20 response rate was consistent (67% for each subgroup; Table 3). Even among the 110 patients who had no response to prior infliximab treatment, 59% achieved an ACR20 response during adalimumab treatment, as did 41% of the 63 patients who had no response to prior etanercept treatment. For patients who were intolerant of prior TNF-antagonist therapy, ACR50, ACR70 and moderate EULAR responses were similar to the responses observed in TNF-antagonist-naïve patients (Table 3).

After 12 weeks of adalimumab treatment, mean changes in other measures of disease activity, including tender and swollen joint counts, pain and physician's global assessment of disease, were similar among groups (Table 3). Even in patients who had no

response to prior TNF-antagonist therapy, clinically meaningful improvements in measures of disease activity occurred during adalimumab treatment. These changes were of similar magnitude between patients with and without previous anti-TNF treatment.

### Safety

A similar percentage of patients who were naive to TNF-antagonist treatment (72%) and patients previously treated with TNF antagonists (76%) reported an AE. Serious AEs were reported in 13% of patients without and in 18% of patients with a history of anti-TNF treatment. Withdrawals because of AEs during ReAct were similar in the TNF-antagonist-naïve group (10%) and the prior TNF-antagonist group (13%) (Table 2). Serious lupus-related AEs were reported in two TNF-antagonist-naïve patients and in no prior TNF-antagonist patients. Adjusting for exposure time, demyelinating disorder (including two events of central demyelination) occurred at a rate of 0.1/100 patient-years (100 PYs) in the TNF-antagonist-naïve subgroup; there were no demyelinating disorders reported for patients in the prior TNF-antagonist group. The malignancy rate in the TNF-antagonist-naïve group (1.1/100 PYs) was similar to that of the prior TNF-antagonist group (1.4/100 PYs). Overall, for the 6610 patients in ReAct, the standardized incidence ratio of malignancy was 0.71 and the standardized mortality ratio was 1.07 [29].

During treatment with adalimumab, serious infections occurred more frequently in patients who had received prior TNF-antagonist treatment (10.0/100 PYs) compared with TNF-antagonist-naïve patients (4.9/100 PYs). The univariate analysis identified age, sex, duration of RA, diabetes, pulmonary disease, cardiovascular disease, number of previous DMARDs, baseline HAQ DI score and a history of TNF-antagonist treatment for inclusion into the backward selection process of the multiple Cox regression to determine prognostic factors for serious infection. The following predictors for serious infection were identified in the final model: age [hazard ratio per year (HR): 1.02 (95% CI, 1.01–1.03),  $P < 0.0073$ ], male sex [HR 1.48 (95% CI 1.07–2.06),  $P < 0.0187$ ], pulmonary disease [HR 1.53 (95% CI 1.14–2.06),  $P < 0.0048$ ], cardiovascular disease (excluding peripheral vessel disorders) [HR 1.43 (95% CI 1.06–1.93),  $P < 0.0179$ ] and baseline HAQ DI score [HR 1.42 per unit (95% CI 1.14–1.77),  $P < 0.0017$ ]. A history of TNF-antagonist treatment did not reach statistical significance in the multiple regression analysis. There was no difference in the incidence of tuberculosis infections between patients who had (0.4/100 PY) or had not received prior TNF-antagonist therapy (0.5/100 PY).

Based on an analysis of AEs/100 PYs, allergic AEs (including allergies that were considered not related to adalimumab by the investigator) occurred more frequently in the prior TNF-antagonist group (6.5/100 PYs) compared with the TNF-antagonist-naïve group (4.3/100 PYs). Of note, the percentage of patients reporting a medical history of any drug allergy was higher in patients with previous TNF-antagonist exposure (28%, 247/899) compared with TNF-antagonist-naïve patients (17%, 971/5711). Of those 591 patients who had previously received infliximab, 12 (2.0%) patients had an allergic reaction that was considered at least possibly related to adalimumab by the investigator; in 7 of these 12 patients, a medical history of allergy was documented. In 2 patients (0.3%) the allergic event was serious. Of the 188 patients who were previously treated with etanercept, two (1%) patients had a non-serious allergic AE and two (1%) patients had serious allergic AEs that were at least possibly related to adalimumab. The reason for discontinuation of the prior TNF antagonist in 103 patients was specified by the investigator as an allergic condition (including infusion-related reactions but excluding local injection-site reactions), and six of 103 patients developed an allergic reaction (defined by the MedDRA High Level

Group Term ‘allergic conditions’) that was at least possibly related to adalimumab. For three patients, the allergic AE was considered serious. No serious anaphylactic responses were reported in ReAct.

### Discussion

ReAct is the largest study of a TNF antagonist and was designed as an open-label trial to mimic routine care of patients with RA. Results of the study indicate that adalimumab is effective and well-tolerated in RA patients who had previously been treated with infliximab and/or etanercept. After therapy with adalimumab as the second or third TNF antagonist, 60% of patients had an ACR20 response, 76% had at least a moderate EULAR response and 33% of these patients achieved an ACR50 response. Of note, these patients had more severe disease at baseline compared with the TNF-antagonist-naïve group, 70% of whom achieved an ACR20 response at week 12. Over time, the percentage of patients who achieved an ACR50, ACR70, or good EULAR response was sustained and increasing.

Of particular clinical relevance is the finding that adalimumab was effective when used as the third TNF antagonist; 46% of these 120 difficult-to-treat patients achieved an ACR20 response, 62% achieved at least a moderate EULAR response and the global disease activity was assessed as improved in 44% of these patients by the treating rheumatologist. Patients who had previously received etanercept exclusively had a somewhat lower ACR20 response and less improvement in the HAQ DI score compared with patients who had received infliximab exclusively. Also, the percentage of patients with a documented reason for discontinuation of a previous TNF antagonist who discontinued their previous anti-TNF therapy because of no response was higher (42%) in the etanercept group than in the infliximab group (22%). At study entry, patients with prior etanercept treatment had higher disease activity and more limitations in physical function, and the percentage of patients in the prior etanercept-only group who were not receiving concomitant DMARDs was twice as high as that of the prior infliximab-only group. These factors may contribute to the differences in response rates between the two groups in the current study. However, results of adalimumab effectiveness as measured by ACR50, ACR70 and EULAR responses and by percent reduction in DAS28 were similar for patients switching from etanercept and patients switching from infliximab.

Adalimumab effectiveness varied by the reason for discontinuation of the prior TNF antagonist. All measures of disease activity indicated that patients who had been intolerant of prior TNF-antagonist therapy achieved response rates similar to TNF-antagonist-naïve patients. Clinically meaningful improvements in patients with no response to prior TNF-antagonist treatment were demonstrated during adalimumab treatment, with 59% of patients who had no response to infliximab and in 41% of patients who had no response to etanercept achieving an ACR20 response at week 12. An ACR20 response was achieved in 67% of patients who discontinued prior infliximab or etanercept treatment because of either loss of efficacy or intolerance.

Although no direct comparator studies have been completed, the efficacy of adalimumab, etanercept and infliximab appear to be similar for the treatment of RA based on a review of results from placebo-controlled studies; 60–70% of patients who do not respond to methotrexate treatment achieve an ACR20 response with TNF-antagonist treatment [42]. Published reports support switching among TNF antagonists as a rational therapeutic strategy for RA patients. In a non-blinded, open-label retrospective analysis of 70 patients who had received at least two TNF antagonists, 45% of patients switching from an antibody to a soluble receptor antagonist or *vice versa* had a good clinical response (defined as a reduction in the DAS28 of at least 1.2 units after 12 weeks of treatment) to the second TNF antagonist [12].

In 20 patients who had received three TNF antagonists, the third agent was effective in 35% of patients (7 of 20) [12]. In our study, adalimumab as the third TNF antagonist was effective as measured by ACR20 at week 12 in nearly half of the patients. Even in a subgroup of 22 patients (data not shown) who were non-responders to both infliximab and etanercept, 33% achieved an ACR20 response to adalimumab and more than half had at least a moderate EULAR response at week 12.

At present, published reports of reciprocal TNF-antagonist treatment have studied fewer patients than the current analysis. Significant clinical benefit has been reported in patients switching from infliximab to etanercept [17, 19, 21, 22, 24–27], etanercept to infliximab [17, 20, 26], etanercept to adalimumab [16, 18] and infliximab to adalimumab [13–16, 18, 23]. Studies that have compared use of adalimumab as the first TNF antagonist vs the second TNF antagonist in patients who are well-matched for disease severity at baseline demonstrate similar ACR20 responses for both groups (70–78%) [13, 16]. Overall, these studies report few discontinuations because of lack of efficacy or AEs after switching TNF antagonists [13–27]. In observational studies, >60% of patients with rheumatic diseases who had been switched from one TNF antagonist to another continued treatment with the second agent for at least 1 yr after switching [11, 12]. In ReAct, adalimumab treatment continuation rates were similar regardless of the reason for discontinuation of a prior TNF antagonist, with a trend towards longer continuation in patients who had experienced a loss of response to prior anti-TNF therapy. The results obtained with our large cohort of patients ( $n=899$ ) support these previous reports and provide further evidence that failure of one TNF antagonist does not appear to predict a poor response or intolerance to another.

Failure with a TNF antagonist does not necessitate a change in therapeutic class to achieve optimal treatment of RA. Six months of treatment with abatacept, a selective co-stimulation modulator, was associated with an ACR20 response in 50% and ACR50 response in 20% of patients who did not respond to TNF antagonists [43]. Similarly, a 24-week study of rituximab, which depletes CD20-positive B cells, in patients with RA (one-third of whom had failed prior TNF-antagonist therapy) demonstrated an ACR20 response in 55% and an ACR50 response in 34% of patients [44]. It should be noted, however, that the abatacept and rituximab studies were both randomized, blinded, placebo-controlled designs, whereas the current study was an open-label design. The clinical results of the current study, together with the significant inhibition of radiographic progression demonstrated in randomized controlled trials of TNF antagonists, indicate that switching among TNF antagonists may be a viable choice among the various therapeutic options for the treatment of RA. The pharmacological differences of the three available TNF antagonists provide only a partial explanation of successful switching between these agents, all of which target the same mediator of inflammation. Lack or loss of efficacy may be caused by anti-drug antibodies which form complexes and promote rapid clearance of the TNF antagonist [45]. Given the unique structure of each TNF antagonist, the anti-drug antibodies generated against any one TNF antagonist are unlikely to cross react with other TNF antagonists, thus enabling an alternate agent to be efficacious. In addition, varying local TNF concentrations may contribute to diverse susceptibility to TNF inhibition among patients. However, the immunogenic and pharmacokinetic basis of the effectiveness of one TNF antagonist after failure of another TNF antagonist deserves further study.

The current study has some limitations. First, it was designed as an open-label study to reflect how RA is treated in typical clinical practice. While the design provides insight into what clinical outcomes might be expected in an uncontrolled setting, it does not provide a control arm for objective comparison. Second, we used the last observation, irrespective of the time-point, to describe the extension-phase data because patients discontinued from ReAct

(per protocol) at different time points. A slight trend towards greater clinical benefit cannot be excluded because of the varying adalimumab exposure periods that are not accounted for by use of last observation data. Finally, the study did not evaluate the effectiveness of re-treatment with the same TNF antagonist after an initial therapy failure. Because prior TNF-antagonist treatment failure was determined retrospectively by clinical investigators without use of an objective criterion (such as a lack of ACR20 or DAS28 response), it cannot be certain that patients who failed prior TNF-antagonist therapy did not actually achieve a clinically meaningful response. Therefore, it is possible that re-treatment with the same TNF antagonist also could have produced improved outcomes in some patients.

Adalimumab was generally well-tolerated, and the discontinuation rate because of AEs during adalimumab treatment among the group of patients previously treated with a TNF antagonist was low [13% (113/899)]. Of the 139 patients who had previously discontinued infliximab because of intolerance, 17% withdrew from adalimumab treatment because of AEs, whereas the corresponding percentage in 40 etanercept-treated patients was 13%. Allergic drug reactions that were considered at least possibly related to adalimumab were predominantly non-serious and rare, occurring in 2.1% (4/188) of patients previously treated with etanercept and in 2.0% (12/591) of patients previously treated with infliximab. No patient with prior anti-TNF treatment had an anaphylactic response to adalimumab. A multiple regression analysis indicated no statistically significantly increased risk of serious infections in patients who received prior TNF antagonists compared with TNF-antagonist-naïve patients. No indicators for induction of autoimmune disorders, demyelinating disorders, or congestive heart failure in patients with a history of etanercept and/or infliximab therapy were apparent in this study.

## Conclusions

Adalimumab was effective in a large group of 899 patients with moderate to severe RA who previously failed treatment with infliximab, etanercept, or both TNF antagonists. Only minor differences in effectiveness, particularly in the ACR response rates, were evident between patients previously treated with infliximab and those previously treated with etanercept. Over time, more patients who had experienced a loss of initial response to their previous TNF antagonist continued adalimumab treatment compared with patients who had no response or were intolerant of a prior TNF antagonist. Adalimumab was generally safe and well-tolerated in all patient subgroups; there was no additional risk in patients who switched from either etanercept or infliximab to adalimumab. Safety results from this trial are consistent with what had been observed in previous clinical trials of adalimumab in RA. Furthermore, results of this open-label, clinical practice study indicate that adalimumab is an effective treatment of RA for patients who did not respond to or were intolerant of treatment with other TNF antagonists, and suggests a good risk–benefit ratio in this population.

### Rheumatology key messages

- Adalimumab is effective regardless of prior TNF-antagonist use.
- Adalimumab is well-tolerated in patients who were intolerant of etanercept and/or infliximab.
- Adalimumab is effective when used as the third TNF antagonist.

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## References

- 1 Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. *Cochrane Database Syst Rev* 2005;CD005113.
- 2 Genovese MC, Bathon JM, Fleischmann RM *et al.* Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. *J Rheumatol* 2005;32:1232–42.
- 3 St. Clair EW, van der Heijde DM, Smolen JS *et al.* Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;50:3432–43.
- 4 Keystone EC, Kavanaugh AF, Sharp JT *et al.* Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;50:1400–11.
- 5 Breedveld FC, Weisman MH, Kavanaugh AF *et al.* The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;54:26–37.

- 6 van der Heijde D, Klareskog L, Rodriguez-Valverde V *et al.* Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: 2-yr clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 2006;54:1063–74.
- 7 Smolen JS, van der Heijde DM, St. Clair EW *et al.* Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. *Arthritis Rheum* 2006;54:702–10.
- 8 Smolen JS, Han C, Bala M *et al.* Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum* 2005;52:1020–30.
- 9 Lam J, Takeshita S, Barker JE, Kanagawa O, Ross FP, Teitelbaum SL. TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J Clin Invest* 2000;106:1481–8.
- 10 Hochberg MC, Leibold MG, Plevy SE, Hobbs KF, Yocum DE. The benefit/risk profile of TNF-blocking agents: findings of a consensus panel. *Semin Arthritis Rheum* 2005;34:819–36.
- 11 Gomez-Reino JJ, Carmona L. The BIOBADASER Group. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a 4-yr period. *Arthritis Res Ther* 2006;8:R29. Published Online First: doi:10.1186/ar1881.
- 12 Solau-Gervais E, Laxenaire N, Cortet B, Dubucquoi S, Duquesnoy B, Flipo RM. Lack of efficacy of a third tumour necrosis factor (alpha) antagonist after failure of a soluble receptor and a monoclonal antibody. *Rheumatology* 2006;45:1121–4.
- 13 Nikas SN, Voulgari PV, Alamanos Y *et al.* Efficacy and safety of switching from infliximab to adalimumab: a comparative controlled study. *Ann Rheum Dis* 2006;65:257–60.
- 14 Bennett AN, Peterson P, Zain A, Grumley J, Panayi G, Kirkham B. Adalimumab in clinical practice. Outcome in 70 rheumatoid arthritis patients, including comparison of patients with and without previous anti-TNF exposure. *Rheumatology* 2005;44:1026–31.
- 15 van der Bijl AE, Breedveld FC, Antoni CE *et al.* Adalimumab (HUMIRA®) is effective in treating patients with rheumatoid arthritis who previously failed infliximab [abstract SAT0062]. *Ann Rheum Dis* 2005;64(Suppl. III):428.
- 16 Wick MC, Ernestam S, Lindblad S, Bratt J, Klareskog L, van Vollenhoven RF. Adalimumab (Humira) restores clinical response in patients with secondary loss of efficacy from infliximab (Remicade) or etanercept (Enbrel): results from the STURE registry at Karolinska University Hospital. *Scand J Rheumatol* 2005;34:353–8.
- 17 Cohen G, Courvoisier N, Cohen JD, Zaitni S, Sany J, Combe B. The efficacy of switching from infliximab to etanercept and vice-versa in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2005;23:795–800.
- 18 Brocq O, Albert C, Roux C, Gerard D, Breuil V, Ziegler LE. Adalimumab in rheumatoid arthritis after failed infliximab and/or etanercept therapy: experience with 18 patients. *Joint Bone Spine* 2004;71:601–3.
- 19 Haraoui B, Keystone EC, Thorne JC *et al.* Clinical outcomes of patients with rheumatoid arthritis after switching from infliximab to etanercept. *J Rheumatol* 2004;31:2356–9.
- 20 Hansen KE, Hildebrand JP, Genovese MC *et al.* The efficacy of switching from etanercept to infliximab in patients with rheumatoid arthritis. *J Rheumatol* 2004;31:1098–102.
- 21 Gomez-Puerta JA, Sanmarti R, Rodriguez-Cros JR, Canete JD. Etanercept is effective in patients with rheumatoid arthritis with no response to infliximab therapy. *Ann Rheum Dis* 2004;63:896.
- 22 Sanmarti R, Gomez-Puerta JA, Rodriguez-Cros JR, Albaladejo C, Munoz-Gomez J, Canete JD. Etanercept in rheumatoid arthritis patients with a poor therapeutic response to infliximab. *Med Clin (Barc)* 2004;122:321–4.
- 23 Schwartzman S, Fleischmann R, Morgan GJ Jr. Do anti-TNF agents have equal efficacy in patients with rheumatoid arthritis? *Arthritis Res Ther* 2004;6(Suppl. 2):S3–S11.
- 24 Yazici Y, Erkan D. Do etanercept-naïve patients with rheumatoid arthritis respond better to infliximab than patients for whom etanercept has failed? *Ann Rheum Dis* 2004;63:607–8.
- 25 Ang HT, Helfgott S. Do the clinical responses and complications following etanercept or infliximab therapy predict similar outcomes with the other tumor necrosis factor-alpha antagonists in patients with rheumatoid arthritis? *J Rheumatol* 2003;30:2315–8.
- 26 van Vollenhoven R, Harju A, Brannemark S, Klareskog L. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor alpha blockers can make sense. *Ann Rheum Dis* 2003;62:1195–8.
- 27 van Vollenhoven RF. Switching between biological agents. *Clin Exp Rheumatol* 2004;22(5 Suppl. 35):S115–S21.
- 28 Brocq O, Plubel Y, Breuil V *et al.* Etanercept—infliximab switch in rheumatoid arthritis 14 out of 131 patients treated with anti TNF alpha. *Presse Med* 2002;31(39 Pt 1):1836–9.
- 29 Burmester GR, Mariette X, Montecucco CM *et al.* 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. *Ann Rheum Dis* Published Online First: 20 March 2007, doi:10.1136/ard.2006.066761.
- 30 Arnett FC, Edworthy SM, Bloch DA *et al.* American Rheumatism Association 1988 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.



- 31 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.
- 32 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 Criteria. *Arthritis Rheum* 1996;39:34–40.
- 33 Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–8.
- 34 Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the Health Assessment Questionnaire, disability and pain scales. *J Rheumatol* 1982;9:789–93.
- 35 Fransen J, Creemers MC, Van Riel PL. Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. *Rheumatology* 2004;43:1252–5.
- 36 Furst DE, Breedveld FC, Kalden JR *et al.* Updated consensus statement on biological agents for the treatment of rheumatoid arthritis and other rheumatic diseases (May 2002). *Ann Rheum Dis* 2002;61(Suppl. 2):ii2–ii7.
- 37 Furst DE, Breedveld FC, Kalden JR *et al.* Updated consensus statement on biological agents, specifically tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) blocking agents and interleukin-1 receptor antagonist (IL-1ra), for the treatment of rheumatic diseases, 2005. *Ann Rheum Dis* 2005;64(Suppl. 4):iv2–iv14.
- 38 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 STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 2003;30:2563–71.
- 39 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;48:35–45, Erratum in: *Arthritis Rheum* 2003;48:855; *Arthritis Rheum* 2004;22:144.
- 40 Keystone EC, Kavanaugh AF, Sharp JT *et al.* Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;50:1400–11.
- 41 van de Putte LB, 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.
- 42 Hochberg MC, Tracy JK, Hawkins-Holt M, Flores RH. Comparison of the efficacy of the tumour necrosis factor  $\alpha$  blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2003;62(Suppl. 2):13–6.
- 43 Genovese MC, Becker JC, Schiff M *et al.* Abatacept for rheumatoid arthritis refractory to tumor necrosis factor  $\alpha$  inhibition. *N Engl J Med* 2005;353:1114–23, Erratum in: *N Engl J Med* 2005;353:2311.
- 44 Emery P, Fleischmann R, Filipowicz-Sosnowska A *et al.* The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006;54:1390–400.
- 45 van der Laken CJ, Voskuyl AE, Roos JC *et al.* Imaging and serum analysis of immune complex formation of radiolabeled infliximab and anti-infliximab in responders and non-responders to therapy for rheumatoid arthritis. *Ann Rheum Dis* 2007;66:253–6.