

EXTENDED REPORT

The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice

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Background: Randomised controlled trials (RCTs) evaluating the efficacy of antagonists to tumour necrosis factor α (TNF α) showed high response percentages in the groups treated with active drugs.

Objective: To compare the efficacy of anti-TNF treatments for rheumatoid arthritis (RA) patients in RCTs and in daily clinical practice, with an emphasis on the efficacy for patients eligible and not eligible for RCTs of anti-TNF treatments.

Methods: First, randomised placebo-controlled trials written in English for etanercept, infliximab and adalimumab for patients with RA were selected by a systematic review. Second, the DREAM (Dutch Rheumatoid Arthritis Monitoring) register with patients starting for the first time on one of the TNF-blocking agents was used. Patient characteristics, doses of medication and co-medication as well as the ACR20 response percentages were compared between RCTs and DREAM data, stratified for trial eligibility.

Results: In 10 of 11 comparisons, the ACR20 response percentages were lower in daily clinical practice than in the RCT active drug group, which was significant in five of 11 comparisons. Only 34–79% of DREAM patients fulfilled the selection criteria for disease activity in the several RCTs examined. DREAM patients eligible for RCTs had higher response percentages than ineligible DREAM patients. ACR20 response percentages of eligible DREAM patients were comparable with the ACR20 response percentages of the RCT active drug group in 10 of 11 comparisons.

Conclusion: The efficacy of TNF-blocking agents in RCTs exceeded the efficacy of these drugs in clinical practice. However, in clinical practice more patients with lower disease activity were treated with TNF-blocking agents compared with those treated in RCTs. For daily practice patients who were eligible for RCTs, responses were more similar to responses reached in RCTs.

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Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disease with the potential to cause cartilage destruction and bone erosions.¹ To date, the aetiology of RA is unknown. Pro-inflammatory cytokines such as tumour necrosis factor α (TNF α) have been suggested to play a central role in the pathogenesis of the disease.² Inhibition of TNF has been shown to reduce disease activity and to delay the process of progressive joint damage.^{3–5} Presently, three different anti-TNF agents are available for patients with RA: etanercept (Enbrel[®]), infliximab (Remicade[®]) and adalimumab (Humira[®]).

Randomised controlled trials (RCTs) on anti-TNF show high response percentages. It is suggested that comparable efficacy is hardly ever achieved in daily clinical practice.⁶ Differences in efficacy between RCTs and clinical practice might be explained by: patient selection; a wash-out period before inclusion, which artificially increases the disease activity; differences in the doses; co-medication; occurrence of co-morbidity; and adherence.

In the present study, we compared the efficacy of anti-TNF drugs in RA from RCTs with their efficacy in the Dutch Rheumatoid Arthritis Monitoring (DREAM) cohort on anti-TNF (daily clinical practice).

METHODS

We performed a systematic review of RCTs of anti-TNF agents in RA with an emphasis on efficacy parameters as well as data on dose, co-medication and patients' characteristics. The RCT data were compared with the data from the DREAM cohort, reflecting daily clinical practice.

Systematic review

Identification of studies

RCTs (phase III studies) were identified from the Medline database (published before the end of 2005) by using the search strategy for RCTs described in Egger et al.⁷ The search strategy was combined with the following terms to identify relevant studies for our purpose: rheumatoid arthritis and ((etanercept or Enbrel or infliximab or Remicade or adalimumab or Humira) or tumour necrosis factor or TNF)

Based on the title and abstract, all studies that compared etanercept, infliximab or adalimumab with a placebo in the treatment of RA were included, regardless of the concomitant use of methotrexate (MTX). We focused on studies that evaluated treatment groups with a comparable dose and frequency as labelled in the Netherlands (40 mg adalimumab once/2 weeks, 25 mg etanercept twice weekly and 3 mg/kg infliximab per 8 weeks). Only articles written in English were included. Final inclusion and exclusion decisions were made after the articles had been examined. If more than one article from the same study was found, the first article published was included.

Abbreviations: CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; DREAM, Dutch Rheumatoid Arthritis Monitoring; ESR, erythrocyte sedimentation rate; HAS, Health Assessment Questionnaire; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; RCT, randomised controlled trial; TNF, tumour necrosis factor; VAS, visual analogue scale

Data extraction

The included trials were evaluated with respect to patient characteristics, dosage of anti-TNF, MTX and co-medication, and efficacy parameters using predefined data entry forms. Different total joint counts were reported in the articles and the daily clinical practice database. For comparison of baseline characteristics, reported joint counts were converted from number of joints into percentage of joints. The primary efficacy outcome was the percentage of patients with an ACR20 response in the active drug group and in the placebo group.

Daily clinical practice data

In April 2003, a register was started to monitor and evaluate prospectively the use of anti-TNF in patients with RA in 11 hospitals in the Netherlands, the DREAM study on anti-TNF. In the Netherlands, patients are allowed to start with any anti-TNF therapy if they meet the following criteria: (1) diagnosis of RA (according to ACR criteria, 1987⁸); (2) disease activity score (DAS28) >3.2;⁹ and (3) previous treatment with at least two other anti-rheumatics including MTX at an optimal dose (maximum dose of 25 mg/day) or intolerance for MTX. All RA patients in the 11 hospitals starting on anti-TNF for the first time were included in the DREAM register. Patients were treated at the discretion of the attending physician.

Independent trained research nurses assessed patients every 3 months and collected data on patients' demographics, disease activity, treatment, dosages and adverse events. Disease activity was measured using 'core set' measures: 28-joint count for tender and swollen joints, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, the Health Assessment Questionnaire (HAQ), and visual analogue scales (VAS) for general health, disease activity and pain. Additionally, information on patient characteristics and therapeutic setting was available in this register.

Analysis

To compare the patient characteristics, the following variables were analysed: dosage, disease duration, age, gender, rheumatoid factor, percentages of tender and swollen joints, number of prior disease-modifying antirheumatic drugs (DMARDs), and concomitant DMARD, corticosteroid and non-steroidal anti-inflammatory drug (NSAID) use. In order to obtain an indication of the relevance of differences in baseline values between RCTs and DREAM, mean values and SEMs were calculated on the basis of SDs as presented in the articles. Because the joint counts were converted from number of positive joints into percentage of positive joints, SEs of the percentage of joints affected were calculated as the SE of a proportion.

Because the physician global assessment was not present in the DREAM register, modified ACR20 response percentages were calculated as the primary outcome. Modifications were done in two ways. First, the ACR20 response was calculated as a 20% improvement in four out of six parameters, giving an overestimation of the percentage of patients with a response. Second, an underestimation was calculated as a 20% improvement in five out of six parameters. Both ACR20 response percentages are presented in this paper. All efficacy data were analysed as intention-to-treat analyses with a non-responder imputation.

Differences in ACR20 response percentages between the RCTs and the daily clinical practice data were statistically tested for every single RCT. In order to correct for multiple testing of the same hypothesis, we adjusted the significance level by the Bonferroni correction. We hypothesised that the response in daily clinical practice will be less impressive than in the RCTs. Therefore, focus will be on the most conservative comparison of

the overestimation of ACR20 response with the RCT active drug response.

The percentage of patients in daily clinical practice eligible for the RCTs on the basis of the RA activity was calculated for each study. Furthermore, groups of eligible and ineligible patients were compared with the RCT active drug group with regard to the overestimation of the percentage of patients with an ACR20 response.

All analyses were performed using SPSS 12[®].

RESULTS

Systematic review

The search strategy yielded 492 records. On the basis of title and abstract, a total of 27 potentially relevant papers were selected and retrieved to obtain more detailed information. Of these 27 papers, a further 15 were excluded: 13 phase I or phase II studies and two studies of early RA patients. Of the remaining 12 papers, five concerned etanercept,^{4, 10-13} two concerned infliximab^{14, 15} and five concerned adalimumab.¹⁶⁻²⁰ One study^{14, 18} was excluded from the comparison of efficacy because only the response according to the Paulus criteria was presented in the article. All studies except one (Furst et al¹⁸) used a wash-out period of 4 weeks for all DMARDs except MTX in the add-on studies. The follow-up time in the selected studies ranged from 12 to 30 weeks.

DREAM study

By December 2005, 546 patients had been included in the register. Five treatment groups were observed: infliximab with MTX (n = 103), etanercept with MTX (n = 171) and without MTX (n = 45), and adalimumab with MTX (n = 186) and without MTX (n = 31). For the infliximab patients, the mean time of follow-up was 20 months; for all other patients it was 13 months. Baseline characteristics are presented in table 1.

The percentage of patients stopping anti-TNF treatment within 6 months (maximal follow-up time of the included articles) differed for the various treatment approaches: 6.8% stopped in the adalimumab with MTX group, 41.9% in the

Table 1 Patient characteristics in RCTs and the DREAM study

Study	n	Disease duration (months)	Age (years)	% Female	% RF+
Adalimumab + MTX					
Weinblatt, 2003 ¹⁶	67	12.2 (1.4)	57.2 (1.4)	74.6	
Furst, 2003 ¹⁸	318	9.3 (0.49)	55 (0.72)	79.6	63.4
Keystone, 2004 ¹⁷	207	11.0 (0.64)	56.1 (0.94)	76.3	81.6
DREAM study	186	9.6 (0.63)	55.4 (0.93)	66.9	80.1
Adalimumab mono					
Van de Putte, 2003 ¹⁹	70	10.0 (0.84)	52.6 (1.4)	87	91
Van de Putte, 2004 ²⁰	113	10.6 (0.65)	52.7 (1.3)	79.6	79.6
DREAM study	31	13.7 (1.9)	56.0 (2.1)	76.3	81.6
Etanercept + MTX					
Weinblatt, 1999 ¹⁰	59	13	48	90	84
Lan, 2004 ¹¹	29		47.6	83	
DREAM study	171	9.0 (0.77)	55.0 (1.1)	69.1	74.7
Etanercept mono					
Moreland, 1997 ⁴	44	80% >5 years	52	82	
Moreland, 1999 ¹²	78	11	53	74	79
Keystone, 2004 ¹³	153	8.2	52	79	64
DREAM study	45	9.4 (1.0)	55.7 (1.8)	76.3	76.3
Infliximab + MTX					
Maini, 1998 ¹⁴	15	12.1 (2.3)	58.9 (2.6)	67	66.7
ATTRACT, 99-04 ^{15*}	86	8.4 (0.7-45)	56 (25-74)	70	72
DREAM study	103	9.6 (0.9)	58.3 (1.2)	67.9	76.4

DREAM, Dutch Rheumatoid Arthritis Monitoring; MTX, methotrexate; RCT, randomised controlled trial; RF, rheumatoid factor.

Data are presented as means and SE where possible.

*Median values and ranges.

adalimumab monotherapy group, 11.4% in the etanercept with MTX group, 26.7% in the etanercept monotherapy group and 16.5% in the infliximab with MTX group. However, the reasons for stopping—that is, adverse events and lack of effectiveness, were comparable in all groups.

Only minor differences in patient characteristics and ACR core set baseline values between the RCTs and DREAM study were observed (table 1 and table 2). CRP levels, tender joint counts, HAQ, VAS pain and VAS global values were significantly lower in the DREAM data compared with both Van de Putte trials^{19,20}.

Anti-TNF and MTX dosage as well as the use of NSAIDs were comparable. Between 29% and 54% of DREAM patients used corticosteroids, whereas the corticosteroid use in RCTs ranged from 44% to 69%. In RCTs, the prednisone dose was limited to a stable maximal dose of 10 mg/day. In the DREAM patients using corticosteroids, the baseline prednisone dosage was approximately 10 mg/day, but 40% of these patients stopped using it after starting anti-TNF.

Figure 1 presents a graphical display of the effects of anti-TNF on the ACR20 response in DREAM patients, as well as in the RCT active drug group and in the placebo group. The ACR20 response percentages are generally lower in daily clinical practice than in the RCT active drug group. This difference is significant in five of 11 comparisons with an overestimation and in nine of 11 comparisons with an underestimation (table 3). The absolute difference between the RCT active drug group and daily clinical practice varied between 2% and -44% for overestimation and between -11% and -56% for underestimation of ACR20 response percentages. The difference in responses was smallest for adalimumab and largest for etanercept.

Although our results presented in table 1 indicated that the baseline values and patient characteristics were comparable between the RCT and the DREAM population, table 4 shows that only 34–79% of DREAM patients fulfilled the inclusion criteria for baseline disease activity in the RCTs.

Figure 2 presents a graphical display of the effects of anti-TNF on the overestimation of the ACR20 response in DREAM patients eligible and ineligible for the RCTs as well as in the

RCT active drug group and in the placebo group. The number of eligible or ineligible patients is very small in some comparisons (see table 4), giving rise to large standard errors. The ACR20 response percentages in DREAM patients eligible for the RCTs were generally still lower than the response percentages in the RCT active drug groups (fig 2). The difference between the RCTs and eligible DREAM patients was statistically significant in one of 11 comparisons (table 5). The absolute difference between the RCT active drug group and eligible DREAM patients ranged from 14.7% to -35%. The absolute difference between the RCT active drug group and ineligible DREAM patients ranged from -9.4% to -54.8% and was significantly lower in six of 11 comparisons.

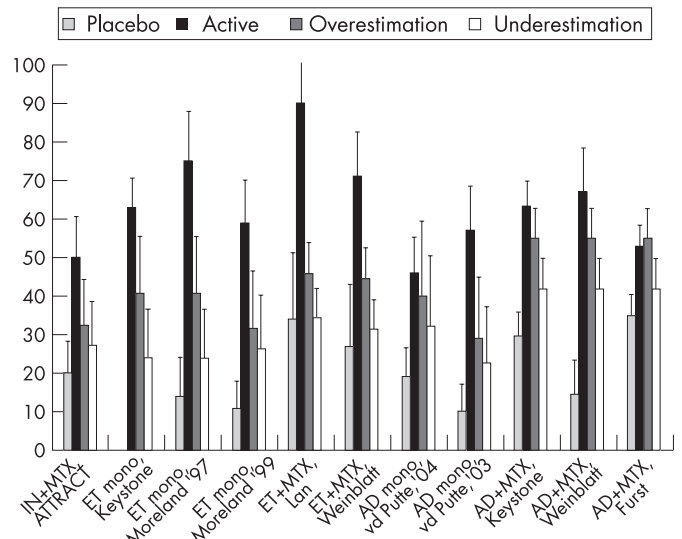


Figure 1 The efficacy of anti-tumour necrosis factor (TNF) in the active drug group (Active) and the placebo group as the percentages of patients with an ACR20 response compared with the overestimation and underestimation of the ACR20 response in daily clinical practice. AD, adalimumab; ET, etanercept; IN, infliximab.

Table 2 ACR core set baseline values in RCTs and the DREAM study

Study	n	SJ*	TJ*	CRP (mg/ml)	HAQ	VAS pain 0–100	VAS DAS 0–100
Adalimumab + MTX							
Weinblatt, 2003 ¹⁶	67	26.2 (5.4)	41.2 (5.9)	21 (2.2)	1.55 (0.07)	53.0 (2.7)	56.9 (2.6)
Furst, 2003 ¹⁸	318	31.7 (5.7)	40.1 (5.9)	15 (1.1)	1.37 (0.03)	55.1 (1.3)	53.9 (1.3)
Keystone, 2004 ¹⁷	207	29.2 (5.6)	40.1 (5.9)	18 (1.6)	1.45 (0.04)	55.9 (1.4)	52.7 (1.5)
DREAM study	186	29.5 (8.6)	32.3 (8.8)	21 (2.0)	1.3 (0.05)	60.2 (1.8)	60.6 (1.6)
Adalimumab mono							
Van de Putte, 2003 ¹⁹	70	28.3 (5.5)	45.6 (6.0)	56 (4.7)	1.74 (0.8)	73.4 (2.3)	64.8 (2.2)
Van de Putte, 2004 ²⁰	113	31.1 (5.7)	50.0 (6.0)	53 (3.5)	1.83 (0.06)	70.1 (1.9)	72.5 (1.8)
DREAM study	31	29.3 (8.6)	30.6 (8.7)	26 (4.9)	1.5 (0.12)	57.3 (3.9)	55.2 (3.5)
Etanercept + MTX							
Weinblatt, 1999 ¹⁰	59	29.4	39.4	22	1.5	50.0	60.0
Lan, 2004 ¹¹	29	47.0 (9.4)	50.0 (9.4)	17	0.99	55.2	66.2
DREAM study	171	36.1 (9.1)	32.3 (8.8)	19 (1.7)	1.3 (0.06)	60.3 (1.9)	59.9 (1.8)
Etanercept mono							
Moreland, 1997 ⁴	44	35.3 (5.8)	42.3 (5.9)	36	1.35	63	65
Moreland, 1999 ¹²	78	36.8 (5.8)	46.5 (5.9)	47	1.6	67	70
Keystone, 2004 ¹³	153	28.2 (5.4)	41.1 (5.6)	19 (5.0)	1.4	53	60
DREAM study	45	36.3 (9.1)	35.7 (9.1)	23 (3.3)	1.5 (0.09)	67.4 (3.9)	68.1 (3.7)
Infliximab + MTX							
Maini, 1998 ¹⁴	15	24.2	30.9	42	2.0	60	65
ATTRACT, 99-04 ¹⁵ †	86	28.8 (20–46)	47.1 (24–68)	31 (13–53)	1.8 (1.4–2.3)	70 (56–81)	66 (49–78)
DREAM study	103	31.3 (8.8)	33.9 (8.9)	27 (4.0)	1.4 (0.08)	58.3 (2.6)	54.7 (2.6)

CRP, C-reactive protein; DAS, disease activity score; DREAM, Dutch Rheumatoid Arthritis Monitoring; HAQ, Health Assessment Questionnaire; MTX, methotrexate; RCT, randomised controlled trial; VAS, visual analogue scale.

*Mean numbers of swollen and tender joints were converted to percentage of swollen and tender joints of the total number of joints counted.

†Median values and ranges (age and disease duration) or interquartile ranges (SJ, TJ and CRP).

All data are presented as means and SEs.

Table 3 The efficacy as the percentage of patients with an ACR20 response of anti-TNF in the active drug group (Active) and daily clinical practice (DREAM)

Study	Active	Follow-up time (weeks)	Overestimation			Underestimation		
			DREAM	Δ	p Value	DREAM	Δ	p Value
Adalimumab + MTX								
Weinblatt, 2003 ¹⁶	67.2	24	54.9	-12.3	0.04411	41.8	-25.4	0.00026
Furst, 2003 ¹⁸	52.8	24	54.9	2.1	0.66326	41.8	-11	0.01383
Keystone, 2004 ¹⁷	63.3	24	54.9	-8.4	0.05409	41.8	-21.5	0.00003
Adalimumab mono								
Van de Putte, 2003 ¹⁹	57	12	29.0	-28.0	0.00470	22.6	-34.4	0.00069
Van de Putte, 2004 ²⁰	46	24	40.0	-6.0	0.29261	32.0	-14.0	0.10066
Etanercept + MTX								
Weinblatt, 1999 ¹⁰	71	24	44.5	-26.5	0.00029	31.5	-39.5	0.00000
Lan, 2004 ¹¹	90	12	45.7	-44.3	0.00001	34.4	-55.6	0.00000
Etanercept mono								
Moreland, 1997 ⁴	75	12	40.5	-34.5	0.00059	23.8	-51.2	0.00000
Moreland, 1999 ¹²	59	24	31.6	-27.4	0.00280	26.3	-32.7	0.00047
Keystone, 2004 ¹³	63	16	40.5	-22.5	0.00442	23.8	-39.2	0.00000
Infliximab + MTX*								
ATTRACT, 99-04 ¹⁵	50	30	32.2	-17.8	0.01665	27.1	-22.9	0.00291

DREAM, Dutch Rheumatoid Arthritis Monitoring; MTX, methotrexate; RCT, randomised controlled trial; RF, rheumatoid factor. Bonferroni correction resulted in a p value <0.0045 (0.05/11) being considered significant. *Maini et al¹⁴ presented only Paulus criteria in their articles.

DREAM patients who were eligible for the RCTs had higher response rates than ineligible patients. The absolute difference between the eligible and ineligible patients ranged from -9.6% to 44.2% in favour of the eligible patients, but was significantly higher in two comparisons.

DISCUSSION

Our data confirm the impression that in clinical practice the effects of anti-TNF treatment are smaller than in published RCTs. In five of 11 comparisons there was a significant difference between the daily clinical practice data and the active drug group of the RCTs. Further, the data indicate that selection towards high disease activity in RCTs is a major explanation for the observed difference in efficacy. This can be concluded from the fact that the differences in response between the active drug groups and the eligible patients were smaller than the differences between the active drug groups and the ineligible patients. Furthermore, eligible patients had up to 44% higher response rates than ineligible patients.

With respect to dosing regime and co-medication, a difference in the use of corticosteroids between daily clinical practice and RCTs was observed. In clinical practice, fewer patients used prednisone and many patients stopped prednisone

after starting anti-TNF therapy. This might be another explanation for the lower efficacy of anti-TNF in clinical practice compared with the efficacy in RCTs.

Our results confirm the observation by Sokka and Pincus,²¹ who showed that most patients receiving routine care did not meet the inclusion criteria for the early RA trial of etanercept (ERA) and the ATTRACT study (42% and 5%, respectively, did meet the criteria). However DREAM patients fulfilled the inclusion criteria for disease activity more frequently, which is probably explained by the fact that their routine care cohorts consisted of all RA patients instead of RA patients who started anti-TNF therapy. Zink and colleagues also showed that eligible patients had higher response rates than non-eligible patients.²²

Wolfe and Michaud concluded that the design of RCTs exaggerates the anti-TNF treatment effect due to a wash-out, patient selection and regression to the mean.²³ This finding is confirmed by our result showing that daily clinical practice patients eligible for the RCTs have a larger response than patients ineligible for the RCTs. Wolfe and Michaud suggested that the efficacy of new drugs observed in RCTs should be corrected for the active comparators by subtracting the placebo response from the response in the RCT active drug group.²³ This could be possible if the clinical effect of the placebo itself is

Table 4 Percentage of DREAM patients eligible for the RCTs on the basis of disease activity

Study	Criteria for active RA in RCTs	No. of eligible DREAM patients (%)
Adalimumab + MTX		
Weinblatt, 2003 ¹⁶	$\geq 9/68$ TJ, $\geq 6/66$ SJ	146/186 (78.5%)
Furst, 2003 ¹⁸	$\geq 6/68$ TJ, $\geq 6/66$ SJ	138/186 (74.2%)
Keystone, 2004 ¹⁷	$\geq 9/68$ TJ, $\geq 6/66$ SJ, CRP >1 mg/dl, RF+	61/186 (32.8%)
Adalimumab mono		
Van de Putte, 2003 ¹⁹	$\geq 12/68$ TJ, $\geq 10/66$, ESR ≥ 28 or CRP ≥ 2 mg/dl	9/31 (29.0%)
Van de Putte, 2004 ²⁰	$\geq 12/68$ TJ, $\geq 10/66$, ESR ≥ 28 or CRP ≥ 2 mg/dl	9/31 (29.0%)
Etanercept + MTX		
Weinblatt, 1999 ¹⁰	$\geq 6/71$ TJ, $\geq 6/68$ SJ	126/171 (73.7%)
Lan, 2004 ¹¹	$\geq 6/28$ TJ, $\geq 6/28$ SJ	87/171 (50.9%)
Etanercept mono		
Moreland, 1997 ⁴	$\geq 12/71$ TJ, $\geq 10/68$ SJ, ESR ≥ 28 or CRP >2 mg/dl	18/45 (40.0%)
Moreland, 1999 ¹²	$\geq 12/71$ TJ, $\geq 10/68$ SJ, ESR ≥ 28 or CRP >2 mg/dl	18/45 (40.0%)
Keystone, 2004 ¹³	$\geq 6/71$ TJ, $\geq 6/68$ SJ	36/45 (80.0%)
Infliximab + MTX		
Maini, 1998 ¹⁴	$\geq 6/68$ TJ and at least two of the following $\geq 6/66$ SJ, ESR >28, CRP >1.5 mg/dl	49/103 (47.6%)
ATTRACT, 99-04 ¹⁵	$\geq 6/68$ TJ, $\geq 6/66$ SJ, ESR >28 or CRP >2 mg/dl	44/103 (42.7%)

CRP, C-reactive protein; DREAM, Dutch Rheumatoid Arthritis Monitoring; ESR, erythrocyte sedimentation rate; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomised controlled trial; RF, rheumatoid factor; SJ, swollen joints; TJ, tender joints.

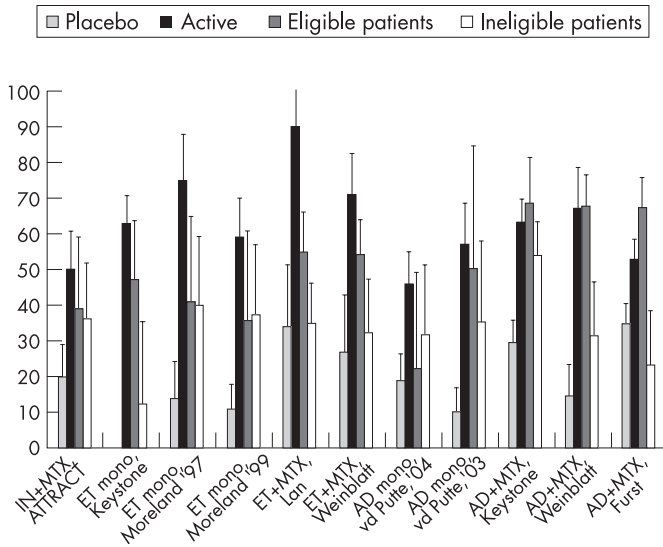


Figure 2 The efficacy of anti-tumour necrosis factor (TNF) in the active drug group (Active) and the placebo group as the percentages of patients with an ACR20 response compared with the overestimation of the ACR20 response in eligible and ineligible daily clinical practice patients. AD, adalimumab; ET, etanercept; IN, infliximab.

zero. It has been proven that this is not the case in subjective continuous outcomes, especially measures of pain.²⁴ Five out of seven ACR core set measures are subjective outcome measures or consider pain. Therefore, the placebo response is a combination of the placebo effect itself and other effects, such as patients' preferences and regression to the mean. These placebo effects are different in every trial and observational setting,

therefore it is not possible to develop an algorithm to correct the efficacy shown in RCTs for the expected effectiveness in daily clinical practice. Therefore, we illustrate the difference between clinical practice and RCTs by describing the possible confounding issues and their magnitude as observed.

This study has limitations. For our data collection we only counted 28 joints instead of 68 as in most RCTs. This might result in an overestimation of the baseline disease activity in the observational data because the 28 counted joints are likely to be the 28 joints most affected in RA.²⁵ Next, patients in daily clinical practice are treated with the medication of preference. We consider it probable that this can result in a larger treatment effect than in RCTs.^{26, 27} We were unable to calculate the exact ACR20 response criteria as was done in most selected papers. Instead, we had to compare the efficacy of anti-TNF on an overestimation or underestimation of the ACR20 response, which makes interpretation more difficult.

RCTs are the appropriate design to evaluate efficacy of new interventions. However, observational phase IV studies have a complementary value to investigate long-term side effects and efficacy, and may be useful to study effects in patients not typically included in phase III RCTs.²⁶

This study confirms the impression that in clinical practice the effects of anti-TNF are smaller than in published RCTs. For daily practice patients who were eligible for RCTs, responses were more similar to responses reached in RCTs. Responses were lower in patients ineligible for RCTs. Selection towards high disease activity and the continued use of co-medication in RCTs are probable explanations for the difference in effects of anti-TNF in clinical practice and in RCTs.

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Table 5 The efficacy as the overestimated percentage of patients with an ACR20 response to anti-TNF in the active drug group (Active) and the DREAM patients, eligible and ineligible for the RCTs

Study	Active	Eligible DREAM patients				Ineligible DREAM patients			
		n	ACR20	Δ	p Value*	n	ACR20	Δ	p Value*
Adalimumab + MTX Weinblatt, 2003 ¹⁶	67,2	115	67.8	0.6	0.5332	38	31.6†	-35.6	
Furst, 2003 ¹⁸	52,8	123	67,5	14.7	0.9971	30	23.3†	-29.5	0.0002
Keystone, 2004 ¹⁷	63,3	51	68.6	5.3	0.7605	102	53.9	-9.4	0.0562
Adalimumab mono Van de Putte, 2003 ¹⁹	57	9	50.0	-7.0	0.3527	17	35.3	-21.7	0.0540
Van de Putte, 2004 ²⁰	46	8	22.2	-23.8	0.0833	22	31.8	-14.2	0.1096
Etanercept + MTX Weinblatt, 1999 ¹⁰	71	109	54.1	-16.9	0.0164	37	32.4	-38.6	0.0001
Lan, 2004 ¹¹	90	80	55.0	-35.0	0.0004	71	35.2	-54.8	0.0000
Etanercept mono Moreland, 1997 ⁴	75	14	41.2	-33.8	0.0064	25	37.5	-35.0	0.0020
Moreland, 1999 ¹²	59	17	35.7	-23.3	0.0531	24	40.0	-21.5	0.0323
Keystone, 2004 ¹³	63	34	47.1	-15.9	0.0434	8	12.5	-50.5	0.0022
Infliximab + MTX‡ ATTRACT, 99-04 ¹⁵	50	23	39.1	-10.9	0.1763	36	36.1	-13.9	0.0799

DREAM, Dutch Rheumatoid Arthritis Monitoring; MTX, methotrexate; RCT, randomised controlled trial.

*Bonferroni correction resulted in a p value <0.0045 (0.05/11) being considered significant compared with the active drug group.

†Significant (p value <0.0045 (0.05/11)) difference between response percentages of eligible and ineligible patients.

‡Maini et al¹⁴ presented only Paulus criteria in their articles.

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