

Original article

Comparative effectiveness and predictors of response to tumour necrosis factor inhibitor therapies in rheumatoid arthritis

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Abstract

Objectives. Adalimumab, etanercept and infliximab are effective TNF inhibitors (TNFis) in the treatment of RA, but no randomized clinical trials have compared the three agents. Prior observational data are not consistent. We compared their effectiveness over 1 year in a prospective cohort.

Methods. Analyses were performed on subjects' first episode of TNFi use in the Rheumatic Diseases Portuguese Register, Reuma.pt. The primary outcome was the proportion of patients with European League Against Rheumatism good response sustained at two consecutive observations separated by 3 months during the first year of TNFi use. Comparisons were performed using conventional adjusted logistic regression, as well as matching subjects across the three agents using a propensity score. In addition, baseline predictors of treatment response to TNFi were identified.

Results. The study cohort included 617 RA patients, 250 starting etanercept, 206 infliximab and 161 adalimumab. Good response was achieved by 59.6% for adalimumab, 59.2% for etanercept and 51.9% for infliximab ($P=0.21$). The modelled probability of good response did not significantly differ across agents (etanercept vs adalimumab OR=0.97, 95% CI 0.55, 1.71; etanercept vs infliximab OR=1.25, 95% CI 0.74, 2.12; infliximab vs adalimumab OR=0.80, 95% CI 0.47, 1.36). Matched propensity score analyses also showed no significant treatment response differences. Greater educational attainment was a predictor of better response, while smoking, presence of ACPA, glucocorticoid use and worse physician assessment of disease activity at baseline each predicted a reduced likelihood of treatment response.

Conclusion. Over 1 year, we found no difference in effectiveness between adalimumab, etanercept and infliximab.

Key words: RA, TNF inhibitors, comparative effectiveness, Reuma.pt register, response predictors.

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Introduction

TNF inhibitor (TNFi) therapies are the most frequent first choice biologic therapy for RA patients and their effectiveness is well established [1–4]. Over the past decade multiple studies on anti-TNF therapies have been done, but until now only a study from Hetland *et al.* [5] specifically addressed comparative response rates among these three agents. In this study, adalimumab presented higher response and remission rates and etanercept longer survival retention time. However, in a study from the British Biologics Register assessing predictors of treatment response, Hyrich *et al.* [6] found no difference in overall response between etanercept and infliximab. Thus there is still a lack of strong evidence to support informed selection among TNFis. No randomized clinical trials (RCTs) are available comparing the three agents. Patients who become refractory or experience an adverse event might benefit from switching to another TNFi, suggesting that slight molecular differences have practical clinical consequences [7–10]. In the absence of head-to-head RCTs, confirmatory carefully designed observational studies are required to address this question.

The primary aim of this work was to evaluate the comparative effectiveness of adalimumab, etanercept and infliximab in the treatment of RA during 1 year of follow-up in clinical practice using conventional multivariate logistic regression and sensitivity analysis with propensity-matched cohorts. Our secondary aim was to look for baseline clinical predictors of treatment response to these TNFis.

Patients and methods

Patients

Analyses were performed upon Reuma.pt, the Rheumatic Diseases Portuguese Register from the Portuguese Society of Rheumatology (SPR), which captures more than 90% of patients treated with biologic therapies managed in rheumatology departments across Portugal [11]. RA patients fulfilling the ACR 1987 revised criteria [12] were eligible for this study if they had at least 6 months of follow-up and were evaluated at two time points separated by 3 months after the start of their first TNFi. Patients who did not accomplish this were excluded and were not taken into account in the denominator for the response rate calculation. Patients were also excluded from these analyses if they had been previously treated with other biologic therapies.

TNFi therapy has been available in Portugal since 2000, with a balanced prescription distribution for etanercept and infliximab. In 2003 adalimumab was also licensed for use. All drugs were reimbursed by the Portuguese National Health Service. The decision to initiate and maintain the treatment is guided by the SPR's recommendations [13]. There is no guidance on which TNFi agent should be used first.

Reuma.pt was approved by the National Board of Data Protection and Health National Directorate. Written

informed consent was obtained from all patients. This study was conducted in accordance with the regulations governing clinical trials, such as the Declaration of Helsinki as amended in Seoul (2008), and was approved by the Santa Maria Hospital Ethics Committee.

Outcome measurements

The primary outcome was the proportion of subjects with sustained good response across each of the three TNFis maintained in two consecutive evaluations separated by 3 months, as defined by the European League Against Rheumatism (EULAR) criteria for good response, i.e. $\text{DAS-28} \leq 3.2$ and $\Delta\text{DAS-28} > 1.2$ [14]. Secondary outcomes included the average time to achieve EULAR good response to adalimumab, etanercept and infliximab; i.e. the proportion of patients achieving at each time point DAS-28 remission ($\text{DAS-28} < 2.6$), clinical disease activity index remission ($\text{CDAI} \leq 2.8$) and simplified disease activity index remission ($\text{SDAI} \leq 3.3$) [15, 16].

Covariates

The data collected at baseline included sociodemographics, RA disease characteristics, comorbidities and treatments. Sociodemographic factors collected were age at RA onset, age at TNFi start, gender, number of years of education and smoking (never/ever). Variables related to RA consisted of erosive disease (the presence of any erosion on X-rays of the hands or feet), RF, ACPA and the presence of any extra-articular manifestations. Comorbidities considered were hypertension, hyperlipidaemia, diabetes and cardiovascular disease. Concomitant therapies consisted of glucocorticoids and synthetic DMARDs. In addition, the following variables were collected at inclusion and at each follow-up visit: tender and swollen joint counts, ESR, CRP, patient's and physician's global assessment of disease activity and HAQ.

Statistical analyses

We compared baseline characteristics across the three TNFi cohorts, using ANOVA followed by Bonferroni tests when significant differences were detected across continuous variables and chi-square tests for categorical baseline characteristics. Unadjusted chi-square tests or ANOVA were used to compare outcome variables, including the proportion of EULAR good response at each time point, time to treatment response and proportion achieving remission. The probability of response was modelled, comparing the three TNFis in a single model. The primary analyses were performed by multivariate logistic regression models predicting response during the first year of treatment. The results of these analyses are presented as an odds ratio (OR) with 95% CIs. Candidate covariates were entered in the multivariate model if $P < 0.2$ in univariate analysis or if they were considered clinically relevant (disease duration, RF and ACPA). A global model with all variables and stepwise backward models with a significance level < 0.05 were performed. Adalimumab was used as reference when compared with etanercept and

infliximab. Missing values were not replaced, as they represented <5%, taking individual covariates by drug.

In addition to the conventional logistic regression analysis, we performed a sensitivity analysis using a propensity score. A propensity score is the probability of using one treatment compared with another [17]. The propensity scores were estimated using logistic regression models that included all covariates. We used a 1:1:1 nearest neighbour propensity score algorithm to match patients across the three TNFi cohorts [18]. After creating the propensity score matched cohorts, response rates were compared using chi-square tests.

A secondary analysis examined baseline predictors of treatment response to TNFis using multivariate logistic regression models. The three TNFis were treated as a group and we considered all covariates. We also explored baseline predictors of response to each TNFi in three separate logistic models. All data were analysed using SAS version 9.2 (SAS Institute, Cary, NC, USA). A two-sided $P < 0.05$ was considered significant.

Results

Baseline data

The potentially eligible patients from Reuma.pt included 2077 with RA. Application of the inclusion and exclusion criteria identified 632 eligible TNFi first-time user patients (Fig. 1). Fifteen of them treated with golimumab were excluded because of the small numbers, leaving 617 for analysis. Demographic and clinical features for each

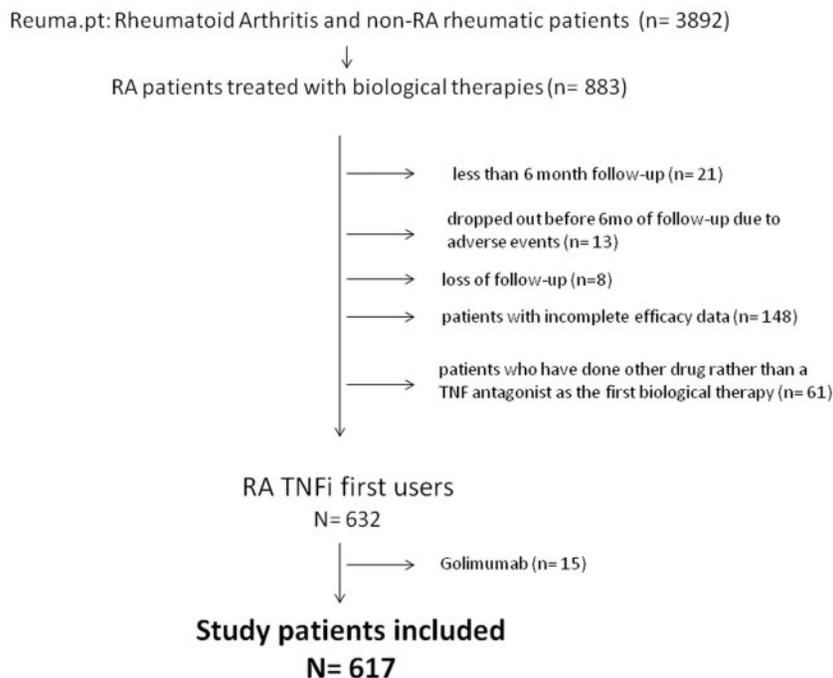
group are described in Table 1. Infliximab-treated patients were significantly older at treatment start, had lower education, more comorbidities and more concomitant therapies.

Treatment responses

Table 2 shows no differences in the proportion of EULAR good responders at 3, 6 and 12 months for each TNFi. The number of EULAR good responders during the first year of follow-up was 148 (59.2%) in the etanercept group, 107 (51.9%) in the infliximab group and 96 (59.6%) in the adalimumab group (unadjusted chi-square test, $P = 0.21$). The time to achieve EULAR good response criteria in the group of responders to TNFi during the first year of therapy was 5.9 ± 3.4 months for etanercept, 7.1 ± 4.6 months for infliximab and 6.4 ± 4.2 months for adalimumab (ANOVA, $P = 0.2$). The remission rate was assessed also at 3, 6 and 12 months for each TNFi using widely accepted clinical remission criteria, DAS-28, CDAI and SDAI. Again, we found no differences in the frequency of remission across TNFi users (Table 3).

For modelling the probability of good response during the first year of treatment, conventional multivariate logistic regression analyses were performed. These models showed no significant differences between the proportion of good responders treated with the three drugs. In adjusted analyses, the probability of good response was similar for etanercept compared with adalimumab (OR=0.97, 95% CI 0.55, 1.71), infliximab compared with adalimumab (OR=0.80, 95% CI 0.47, 1.36), and

Fig. 1 Diagram with patients' assembly.



The number and reasons for patient exclusion are indicated. In the end, 617 patients were included in the analysis.

TABLE 1 Baseline characteristics of 617 first-time users of TNFi therapy treated with adalimumab, etanercept or infliximab in Reuma.pt

	Adalimumab (n = 161)	Etanercept (n = 250)	Infliximab (n = 206)	P-value
Age at disease onset, years	42.2 (12.4)	42.2 (12.6)	43.3 (12.7)	0.62
Age at TNFi start, years	50.9 (12.0) ^a	52.4 (12.1)	54.1 (11.9) ^a	0.04 ^b , 0.01 ^a
Disease duration at TNFi start, years	9.5 (7.6)	10.4 (8.6)	11.2 (9.4)	0.21
Female, n (%)	142 (88.2)	227 (90.8)	175 (84.9)	0.16
White, n (%)	150 (93.2)	238 (95.2)	197 (95.6)	0.69
Erosive, n (%) (n = 599)	122 (77.8)	185 (76.8)	156 (77.6)	0.97
RF, n (%)	126 (78.3)	192 (76.8)	163 (79.1)	0.81
ACPA, n (%) (n = 589)	117 (75.9)	172 (72.6)	150 (75.7)	0.53
Extra-articular manifestations, n (%) (n = 552)	28 (19.8)	62 (27.1)	42 (23.1)	0.14
Working full-time, n (%) (n = 590)	67 (43.5)	80 (33.6)	53 (26.8)	0.06
Body mass index, m ² /kg	26.9 (6.1)	26.2 (4.8)	27.1 (4.4)	0.47
Smoking—ever, n (%) (n = 587)	36 (23.4)	51 (21.6)	45 (22.8)	0.26
Education, years	7.4 (4.7)	7.4 (4.7)	6.3 (4.2)	0.03 ^b
Comorbidities, n (%)	80 (49.7)	98 (39.2)	115 (55.8)	0.007 ^b
Hypertension, n (%)	65 (40.4)	72 (28.8)	90 (43.7)	0.01 ^b
High cholesterol, n (%)	32 (19.9)	42 (16.8)	55 (26.7)	0.06
Diabetes, n (%)	12 (7.4)	15 (6.0)	16 (7.8)	0.77
Cardiovascular diseases, n (%)	15 (9.3)	16 (6.4)	26 (12.6)	0.11
DMARDs, n (%)	139 (86.3)	206 (82.4)	196 (95.1)	0.0001 ^b
MTX concomitant, n (%)	127 (78.9)	184 (73.6)	183 (88.8)	0.0002 ^b
Prednisone or similar, n (%)	100 (62.1)	186 (74.4)	152 (73.8)	0.02 ^b
DAS-28 ESR	5.5 (1.1)	5.8 (1.2)	5.9 (1.1)	0.02 ^b , 0.007 ^a
Tender joint counts	9.8 (7.1) ^a	11.5 (7.3)	12.2 (8.1) ^a	0.05 ^b , 0.01 ^a
Swollen joint counts	7.3 (5.4)	8 (5.4)	8.7 (5.9)	0.15
ESR, mm/1st h	39.2 (25.9)	42.1 (29.6)	42.1 (26.8)	0.65
CRP, mg/l	3.1 (9.2)	2.6 (3.4)	2.7 (3.6)	0.73
Patient global assessment	52.9 (22) ^a	60.4 (20.4) ^c	62.2 (21.1) ^{a,c}	0.005 ^b , 0.002 ^a , 0.009 ^c
Physician global assessment	48.9 (18.9)	54.5 (20.2)	56.4 (18.3)	0.06
HAQ	1.3 (0.6) ^{a,d}	1.55 (0.57) ^d	1.53 (0.62) ^a	0.008 ^b , 0.01 ^a , 0.003 ^d

Values shown are means (s.d.) or n (%). The total number of patients evaluated was 617. In the case of variables with missing values, the actual number analysed is indicated after the variable's name. ^aIndicates a significant difference between infliximab and adalimumab. ^bIndicates a significant two-sided $P < 0.05$ tested by ANOVA or chi-square tests. Significant ANOVA tests were further evaluated by Bonferroni multiple comparison tests. ^cA significant difference between etanercept and infliximab. ^dA significant difference between adalimumab and etanercept. Extra-articular manifestations consisted of SS, s.c. nodules, scleritis, Caplan syndrome, serositis, amyloidosis, Felty syndrome, vasculitis and interstitial lung disease.

TABLE 2 EULAR good response to TNFis adalimumab, etanercept and infliximab, among first-time users

Time of evaluation	Adalimumab (n = 161)	Etanercept (n = 250)	Infliximab (n = 206)	P-value
At 3 months	48 (29.8)	82 (32.8)	47 (22.8)	0.17
At 6 months	64 (39.8)	97 (38.8)	68 (33.0)	0.45
At 12 months	76 (47.2)	117 (46.8)	77 (37.4)	0.20
Achieved during the first year ^a	96 (59.6)	148 (59.2)	107 (51.9)	0.21

Values shown are n (%). Drug response was assessed every 3 months. ^aEULAR good response during the first year was defined as DAS-28 < 3.2 and change in DAS-28 > 1.2 at two consecutive evaluations separate by at least 3 months. P-values were obtained from unadjusted chi-square tests. Adalimumab was administered 40 mg s.c. every other week. Etanercept was administered 25 mg s.c. twice a week or 50 mg s.c. once a week. Infliximab was started at 3 mg/kg i.v. at 0, 2, 6, 14 weeks and every 8 weeks thereafter but could be increased to 5 mg every 6 weeks according to rheumatologist judgement.

etanercept compared with infliximab (OR = 1.25, 95% CI 0.74, 2.12) (Table 4).

In the propensity-matched analyses, the baseline features were similar across TNFis (see Supplementary Table 1, available at *Rheumatology* Online). Similar response rates were observed across all three TNFis: etanercept compared with adalimumab (OR = 1.40, 95% CI 0.45, 4.35), infliximab compared with adalimumab (OR = 1.01, 95% CI 0.28, 3.58) and etanercept compared with infliximab (OR = 1.38, 95% CI 0.38, 4.98) (Table 4).

Predictors of response

In adjusted logistic regression analyses, more years of education was a baseline predictor of EULAR good response across all three TNFis. Smoking, ACPA, concomitant use of

glucocorticoids and worse physician VAS were negatively associated with response (Table 5). Baseline predictors of good response for each TNFi drug were also studied in three separate models for each drug exposure (see Supplementary Table 2, available at *Rheumatology* Online).

Discussion

We evaluated the comparative effectiveness of the three dominant TNFis in the Rheumatic Diseases Portuguese Register, Reuma.pt. In our cohort study we found no significant differences in the proportion of patients achieving EULAR good response criteria across three TNFis. This finding was obtained for sustained response in two consecutive evaluations by two different analytic strategies. In addition, remission rates were similar across TNFis.

As with our study, Hyrich *et al.* [6] did not find overall differences between etanercept and infliximab in the British Biologics Register. However, Hetland *et al.* [5], using data from the Danish Register, reported differences across agents, with adalimumab being the most effective and infliximab the least effective drug. Different genetic backgrounds, population characteristics and analysis strategies may contribute to the differences in results.

We found that baseline clinical variables, including disease severity, were different among groups at the start of TNFi therapy, despite the absence of Portuguese guidance for selection of a specific drug. Infliximab and etanercept were the first biologic therapies licensed for RA in Portugal, and patients with more severe RA received these new therapies. Infliximab-treated patients were older and sicker. This may be explained by the fact that i.v. infliximab administration allows closer patient monitoring and assessment. Moreover, s.c. TNFi increases patient autonomy and was preferred for younger, more educated and active patients.

We analyzed baseline predictors of EULAR good response in TNFi patients and found a significant negative association with smoking, ACPA, glucocorticoids therapy and higher physician VAS. Higher education was

TABLE 3 Rate of remission according to different criteria for TNFis (adalimumab, etanercept and infliximab) first-time users

	Adalimumab (n = 161)	Etanercept (n = 250)	Infliximab (n = 206)	P-value
At 3 months follow-up				
DAS-28	20 (12.4)	41 (16.4)	22 (10.7)	0.37
CDAI	16 (9.9)	24 (9.6)	11 (5.3)	0.35
SDAI	13 (8.1)	21 (8.4)	13 (6.3)	0.80
At 6 months follow-up				
DAS-28	34 (21.1)	50 (20.0)	32 (15.5)	0.45
CDAI	22 (13.7)	37 (14.8)	24 (11.7)	0.75
SDAI	23 (14.3)	34 (13.6)	24 (11.7)	0.86
At 12 months follow-up				
DAS-28	36 (22.4)	64 (25.6)	43 (20.9)	0.63
CDAI	32 (19.9)	47 (18.8)	32 (15.5)	0.70
SDAI	32 (19.9)	45 (18.0)	32 (15.5)	0.72

Values shown are n (%). Remission criteria: DAS-28 < 2.6; CDAI ≤ 2.8; SDAI ≤ 3.3. P-values were obtained by unadjusted chi-square tests.

TABLE 4 Multivariate logistic regression and propensity score matched analyses to assess the probability of EULAR good response during the first year of therapy across TNFis

TNFi	EULAR good response					
	Univariate		Multivariate		Propensity score matched ^a	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Etanercept vs adalimumab	0.98 (0.66, 1.47)	0.41	0.97 (0.55, 1.71)	0.91	1.40 (0.45, 4.35)	0.53
Infliximab vs adalimumab	0.73 (0.48, 1.10)	0.08	0.80 (0.47, 1.36)	0.83	1.01 (0.28, 3.58)	0.78
Etanercept vs infliximab	1.34 (0.93, 1.95)	0.41	1.25 (0.74, 2.12)	0.40	1.38 (0.38, 4.98)	0.54

Adalimumab was the reference drug compared with etanercept and infliximab. Infliximab was the reference drug in comparison with etanercept. The following baseline covariates were included in multivariate logistic models: age, disease duration, gender, education level, smoking, RF status, ACPA status, extra-articular manifestations, comorbidities, DAS-28, physician's global assessment of disease activity, HAQ, concomitant CSs and DMARDs. ^aPropensity score analysis treatment groups were matched for baseline characteristics (Supplementary Table 1, available at *Rheumatology* Online). P-values were obtained by chi-square tests.

TABLE 5 Multivariate logistic regression evaluating baseline predictors of response for the three TNFi drugs

Predictor	OR (95% CI)	P-value
Age	0.99 (0.97, 1.01)	0.53
Disease duration	1.0 (0.91, 1.08)	0.84
Male	1.76 (0.87, 3.54)	0.11
RF	0.99 (0.98, 1.00)	0.05
ACPA	0.97 (0.95, 0.98)	<0.0001*
Extra-articular manifestations	0.98 (0.83, 1.15)	0.84
Smoking	0.98 (0.97, 0.99)	0.009*
Education	1.05 (1.00, 1.10)	0.036*
CSs	0.94 (0.9, 0.98)	<0.0001*
DMARDs	1.01 (0.99, 1.02)	0.54
DAS-28	0.99 (0.97, 1.00)	0.11
VAS physician	0.98 (0.97, 0.99)	<0.0001*
HAQ	0.68 (0.39, 1.18)	0.17

Values shown are OR and 95% CI obtained by multivariate logistic regression. Covariates included in the model were age and disease duration at treatment start, sex (female as reference), RF, ACPA, smoking, extra-articular manifestations, education (years), comorbidities, concomitant CSs, concomitant DMARDs, DAS-28, physician's global assessment of disease activity (VAS physician) and HAQ at baseline. Drug exposure was forced in the model. No interaction terms were included in the final model, due to their pre-tested absence of significance. VAS physician is the physician's global assessment of disease activity measured on a visual analogue scale. * $P < 0.05$.

associated with better response. These findings are consistent and largely confirm prior study results [5, 6, 19, 20], although slight differences and distinct predictors identified across studies might be due to different designs, outcome definitions and population characteristics. Hyrich *et al.* [6] reported lower response rates among smokers treated with infliximab and patients with more disability, whereas concomitant MTX and NSAIDs therapy was associated with better response. Females were less likely to achieve remission. The GISEA study confirmed that more severe disease was negatively associated with response [19]. Kristensen *et al.* [20] reported a positive association between low disability and concomitant DMARDs with better response, but they found no differences in response between genders. In our study, concomitant DMARD, including MTX, was not associated with differences in response, while concomitant use of glucocorticoids predicted worse response. Hetland *et al.* [5] found that young age, low functional status and concomitant glucocorticoids treatment were negative predictors of a clinical response and remission.

Therapeutic effectiveness can be assessed by different methods. RCTs comparing TNFis would provide the most robust efficacy information, but it is not expected that such studies will ever be done. Analysis of register data may be adequate to compare drug effectiveness (not

efficacy) in circumstances where doctors are allowed to choose any therapy and outcome data are collected in a structured manner; this is the case for Reuma.pt. However, the limitations associated with observational cohort studies need to be taken into account. Comments about drug efficacy cannot be derived from studies of observational data. An important potential bias could be the non-random selection of therapies, especially when clinicians select a given TNFi for a specific subgroup. Although we did observe small baseline differences in patient characteristics across TNFis, the multivariate models and propensity matched analyses help to alleviate these imbalances. Another important limitation was that follow-up in these analyses was limited to 1 year; differences between these drugs may occur over a longer follow-up. In return, we required a sustained response in two consecutive visits.

In conclusion, in Reuma.pt we found no significant differences in effectiveness across adalimumab, etanercept and infliximab as assessed by EULAR good response criteria. These results were consistent across conventional multivariate analyses and a sensitivity analysis using propensity scores to compare treatment response. As well, results did not differ across primary (EULAR good response) and secondary (time to achieve response and DAS-28, CDAI and SDAI remission criteria) outcomes. Long-term observational analyses and comparison with other classes of biologic agents would be useful to better support the choice of these drugs in the treatment of inflammatory rheumatic diseases.

Rheumatology key messages

- TNF inhibitor drugs showed comparable effectiveness in RA patients.
- A higher level of education predicted a better treatment response in RA patients.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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