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Predictors of response to anti-TNF-α therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register

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***Background*. Anti-tumour necrosis factor-α (TNF-α) therapies represent an important advancement in therapy for rheumatoid arthritis (RA). However, there remains a proportion of patients who do not improve despite therapy. These drugs are expensive and have the potential of serious toxicity. Therefore, it would be ideal to predict the patients who will respond, so that the use of these drugs can be targetted.**

***Objective*. To identify the clinical factors present at the start of anti-TNF-α therapy that are associated with response at 6 months in patients with RA.**

***Methods*. The British Society for Rheumatology (BSR) Biologics Register collects detailed data on all patients with a rheumatic disease receiving biologic therapy in the UK. We studied all patients with RA who had started etanercept (ETA) or infliximab (INF) and had achieved a minimum 6 months follow-up by 1 October, 2004. The disease status at the baseline and at 6 months was assessed using the Disease Activity Score (DAS28). The response was classified according to the European League against Rheumatism (EULAR) improvement criteria. The effect of baseline characteristics on response was studied using multivariate ordinal logistic regression.**

***Results*. 2879 patients were included in this analysis (1267 ETA, 1612 INF). At the start of therapy, the mean age was 55 yrs, disease duration 14 yrs, baseline DAS28 6.7 and health assessment questionnaire (HAQ) 2.1. In all, 28% of ETA and 86% of INF patients were receiving methotrexate. After 6 months, 18% had a good EULAR response, of whom 9% were considered to be in remission and 50% had a moderate response. There was no overall difference in response rate between the two anti-TNF-α therapies. A higher baseline HAQ score correlated with a lower response rate while a better response was associated with the current use of NSAIDs and the use of methotrexate (MTX), although the latter only reached statistical significance with ETA [OR 1.82 (95% CI 1.38–2.40)]. There was a lower response rate among current smokers, particularly in patients receiving INF [OR 0.77 (95% CI 0.60–0.99)]. Age, disease duration, rheumatoid factor and the previous number of disease-modifying antirheumatic drugs (DMARDs) did not predict response to either drug. However, females were less likely to achieve remission.**

***Conclusions*. These data support an improved outcome among patients receiving MTX in combination with anti-TNF-α therapies. However, the most disabled patients were less likely to respond, despite concurrent MTX. The benefits of NSAIDs may reflect the relative absence of comorbidities in patients who can tolerate these drugs or the continuing presence of reversible inflammatory symptoms. The association of smoking and poor outcome with INF is a novel finding and may reflect alterations in pharmacokinetics. The inability of other baseline disease characteristics to predict the outcome suggests that other factors, including potential genetic differences in drug metabolism, may be influencing the response to anti-TNF-α therapies.**

KEY WORDS: Rheumatoid arthritis, Etanercept, Infliximab, Response.

Introduction

The introduction of the anti-tumour necrosis factor-α (TNF-α) therapies has dramatically improved the treatment for severe rheumatoid arthritis (RA). Randomized placebo-controlled trials (RCT) of both infliximab (INF) [1–4] and etanercept (ETA) [5–8] have demonstrated these therapies to be effective in patients with disease-modifying antirheumatic drug (DMARD)-resistant disease. However, only 50–70% of patients receiving the anti-TNF-α therapy achieved at least an American College of Rheumatology 20 response (ACR20) [9] during clinical trials, suggesting that there remains a significant proportion of patients who do not respond. However, there have been minimal data published regarding those factors that can identify the patients most likely to respond to these therapies.

A meta-analysis of RA clinical trials of traditional DMARDs, including methotrexate (MTX), identified that, in addition to previous DMARD failure, increased disease duration, increased disability and female sex correlated with a lower response rate [10]. Clinical trials of anti-TNF-α therapies have shown that concurrent MTX therapy enhances the efficacy of low-dose INF, although the benefits with higher doses of INF are less clear [4]. In addition, the combination of ETA with MTX appears to be superior to the use of ETA alone, when both are newly started at the same time [8]. However, there are limited data comparing the efficacy between ETA when added to background MTX *vs* ETA as mono-therapy [11].

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Clinical trial data have also demonstrated that disease duration may influence the response, with a lesser improvement in disability among those with the longest disease duration [12]. This might be expected, as increasing disease duration would be associated with more irreversible disease. A trial of INF and ETA in ankylosing spondylitis also identified shorter disease duration as an independent predictor of improvement in disease activity [13]. However, disease duration did not appear to affect the positive impact of INF on radiologic progression in patients with RA [14].

There remains a paucity of data, however, assessing the influence of other baseline demographic and disease factors on the clinical response to anti-TNF-α therapies in RA. However, sample size limitations in clinical trials often limit further subgroup analysis and, therefore, larger longitudinal observation cohorts based on routine clinical practice are needed to address the issue of response prediction. Therefore, using patients enrolled in a large longitudinal observational study of biological therapies in rheumatic diseases, we aimed to identify specific demographic and clinical factors that correlate with the response to ETA or INF at 6 months in patients with RA.

Subjects and methods

Subjects

The subjects for this analysis were selected from the large prospective observational study, the British Society for Rheumatology Biologics Register (BSRBR). The methods of this register have been described in detail elsewhere [15]. This analysis was restricted to the inclusion of those patients registered with the BSRBR who had fulfilled the 1987 ACR criteria for RA [16] and had started therapy with either ETA or INF within 6 months of registration. Only those patients who had reached 6 months of follow-up prior to 1 October, 2004 were considered for the study.

UK national guidelines recommend that anti-TNF-α drugs are to be reserved for patients with active RA [defined as a 28 joint count disease activity score (DAS28) greater than 5.1] despite previous therapy with at least two DMARDs, one of which should be MTX) [17]. ETA is administered as a subcutaneous injection of 25 mg twice weekly. INF is administered at a dose of 3 mg/kg at weeks 0, 2, 6 and 8 weekly thereafter. It is recommended that INF be administered with MTX. The study was approved by the North West Multicentre Research Ethics Committee and all subjects gave their written consent for participation.

Baseline assessment

At the time the biological drug is prescribed, the rheumatologist or rheumatology nurse specialist completes a standardized form that includes details of age, gender, diagnosis and disease duration and items on current disease activity including swollen and tender joint counts (based on 28-joint count), erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) and patient global assessment. Details of the past and present anti-rheumatic therapies and current comorbidities were also recorded. The patient is asked to complete a separate questionnaire which includes smoking history and the health assessment questionnaire (HAQ) adapted for British use [18].

Follow-up

Rheumatologists and patients are each sent a 6 monthly postal follow-up questionnaire. Rheumatologists record the current disease activity (swollen and tender joint count, ESR/CRP and patient global assessment), whether the biological drug has been discontinued and any adverse events. Patients also complete a HAQ.

Analysis

Outcome at 6 months was categorized according to the DAS scores using two approaches. Firstly, based on the European League against Rheumatism (EULAR) Improvement Criteria [19] (Fig. 1), patients were classified into three groups: no response, moderate response and good response, based on their 6-month DAS28 and absolute change in DAS28 from baseline. A good responder must demonstrate an improvement of at least 1.2 units and achieve an absolute score of <3.2. A non-responder will demonstrate an improvement of <0.6 or have a final DAS28 score >5.1. Moderate responses fall in between. Those patients who discontinued their anti-TNF-α therapy prior to the end of the first 6 month follow-up, regardless of reason, were labelled as non-responders. Secondly, patients achieving remission at 6 months were identified and defined according to the EULAR criteria (DAS28 < 2.6) [20].

The predictors of EULAR response at 6 months were modelled using both univariate and multivariate ordinal logistic regression, which models the probability of achieving a higher response category in the presence of each predictor variable. A logistic regression model was constructed to identify independent predictors of remission. The following variables were included in the analysis: age at start of therapy (in 10-yr increments), gender, current smoking status (yes/no), comorbidity (yes/no, see subsequently), disease duration (per 10-yr increments), rheumatoid factor status, baseline DAS28 and baseline HAQ score (both continuous variables), previous number of DMARDs (per drug) and concurrent use of MTX, non-steroidal anti-inflammatory

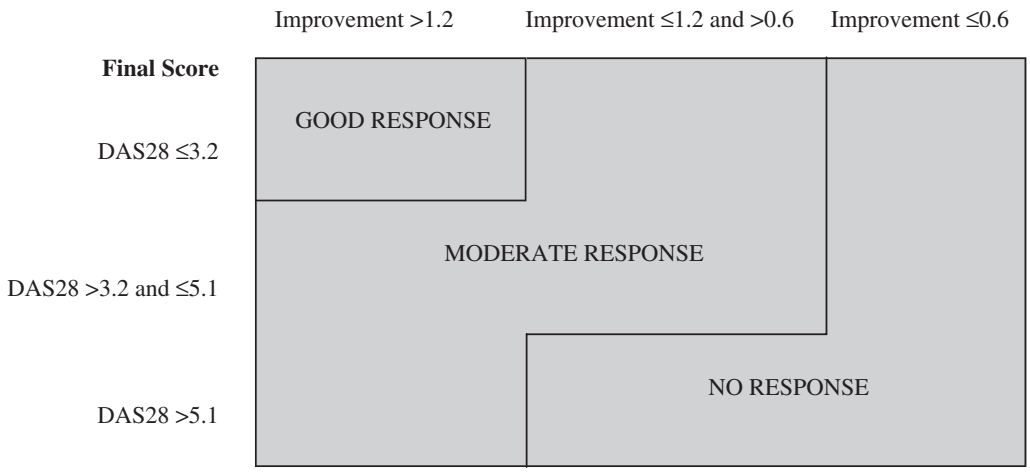

FIG. 1. EULAR improvement criteria.

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TABLE 1. Baseline characteristics

	Etanercept		Infliximab	
	Total	In model[b]	Total	In model[b]
Number	1413	1267	1810	1612
Age (yrs), mean (S.D.)	56 (12)	55 (12)	55 (12)	55 (12)
Female, *n* (%)	1100 (78)	982 (78)	1387 (77)	1232 (76)
Current smokers, *n* (%)	277 (20)	254 (20)	386 (22)	347 (22)
Comorbidity[a], *n* (%)	858 (61)	755 (59)	1038 (57)	919 (57)
Disease duration (yrs), mean (S.D.)	15 (9)	14 (9)	14 (9)	14 (9)
RF positive, *n* (%)	1015 (72)	905 (72)	1308 (72)	1166 (72)
DAS28, mean (S.D.)	6.7 (1.0)	6.7 (1.0)	6.7 (1.0)	6.7 (1.0)
28 SJC, mean (S.D.)	12 (6)	12 (6)	12 (6)	12 (6)
28 TJC, mean (S.D.)	16 (7)	16 (7)	16 (7)	16 (7)
ESR (mm/h), mean (S.D.)	50 (28)	50 (28)	49 (29)	48 (29)
Patient global assessment, mean (S.D.)	72 (20)	72 (20)	72 (20)	72 (20)
HAQ score, mean (S.D.)	2.1 (0.5)	2.1 (0.5)	2.1 (0.5)	2.1 (0.5)
Previous number of DMARDs, mean (S.D.)	4.5 (1.7)	4.4 (1.7)	4.2 (1.7)	4.2 (1.7)
Concurrent NSAIDs, *n* (%)	916 (65)	825 (65)	1200 (66)	1078 (67)
Concurrent corticosteroids, *n* (%)	707 (50)	628 (50)	899 (50)	792 (49)
Concurrent DMARDs, *n* (%)	652 (46)	604 (48)	1683 (93)	1509 (94)
Concurrent MTX, *n* (%)	380 (27)	356 (28)	1538 (85)	1382 (86)
Receiving >1 current DMARD, *n* (%)	161 (11)	155 (12)	368 (20)	343 (21)

[a]Includes hypertension, ischaemic heart disease, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, renal disease, hepatic disease, depression, diabetes and thyroid disease.
[b]See text, i.e. have not discontinued therapy by 6 months for reasons other than inefficacy.

drugs (NSAIDs) or corticosteroids. Comorbidity was based on the presence of one or more of the following conditions: hypertension, ischaemic heart disease, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, renal disease, hepatic disease, depression, diabetes mellitus or thyroid disease. In order to eliminate competing risks, patients who had discontinued therapy prior to the end of the first 6 month follow-up for a reason other than inefficacy were excluded from the model. The results have been presented as the odds ratio (OR) with corresponding 95% confidence interval (CI).

To determine the combined ability of those predictors identified in multivariate analysis to correctly identify EULAR response at 6-months, the patients were assigned a score based on the contribution to the multivariate model of the statistically significant predictors present at baseline. A similar approach was used to predict remission.

Results

By 1 October 2004, 3643 patients from 196 hospitals had completed at least 6 months of follow-up. Of these, 28 patients had died prior to the first 6 month follow-up. A further 392 patients (11%) had some missing data either at the baseline or at 6 months that precluded the calculation of DAS28, leaving 3223 patients (1413 ETA and 1810 INF) eligible for this analysis.

Baseline characteristics

The baseline characteristics, at the start of anti-TNF-α therapy, are presented in Table 1. The mean age of the patients was 55 yrs and 77% of them were female. The mean disease duration was 14 yrs. Baseline disease severity was high. The mean DAS28 was 6.7 (S.D. 1.0) and the mean HAQ score was 2.1 (S.D. 0.5). Half of the cohort was currently receiving corticosteroids. There were no significant differences between the two study drugs.

The mean number of prior DMARDs was 4. The majority of patients (98%) had received MTX at some point during their disease course. However, there were marked differences between the two anti-TNF-α therapies with respect to current MTX use. Eighty-six per cent of patients who started INF were receiving MTX compared with only 28% of patients who started ETA. In total, only 48% of the ETA patients were receiving a concurrent DMARD compared with 94% of the patients starting INF (Pearson $\chi^2 = 872$, $P < 0.001$).

TABLE 2. Details of drug discontinuation prior to first 6 month follow-up[a]

Reason	All (3223)	Etanercept (1413)	Infliximab (1810)
Any reason	614 (19.1)	264 (18.7)	350 (19.3)
Inefficacy	270 (8.4)	118 (8.4)	152 (8.4)
Adverse event	295 (9.2)	129 (9.1)	166 (9.2)
Other	41 (1.3)	12 (0.9)	29 (1.6)
Unknown	8 (0.3)	5 (0.4)	3 (0.2)

[a]Observed differences between etanercept and infliximab are not statistically significant.

Follow up

At the first 6 month follow-up, 81% of patients remained on anti-TNF-α therapy. Approximately 8% of patients discontinued for physician-reported inefficacy, 9% following an adverse event and 2% for a reason unrelated to therapy (Table 2). There were no differences between the two study drugs.

The mean baseline DAS28 fell from 6.7 to 4.6 after 6 months of therapy. Sixty-eight per cent of patients were classified as responders (moderate or good), including the 18% who achieved a good response. Only 9% of patients could be classified as being in remission. The response rate did not differ between the two anti-TNF-α therapies (Table 3).

Predictors of EULAR response

In all, 344 patients (11%) were excluded from the regression model, having discontinued their therapy for a reason other than inefficacy, leaving 2879 patients in the final model (1267 ETA and 1612 INF). Those patients excluded from the analysis were, on average, older (58 *vs* 55 yrs, $P < 0.01$), had a longer disease duration (16 *vs* 14 yrs, $P < 0.01$) and were more likely to have a comorbid disease (64% *vs* 58%, $P = 0.02$) than the other patients.

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The baseline characteristics of patients in the three response categories, by drug, are shown in Table 4. There are no major differences in the distributions of these characteristics between individuals in the response groups. Those most likely to respond were more likely to have used an NSAID, which might suggest a clinically apparent active disease state. On formal regression analysis for both ETA and INF, patients with higher baseline HAQ scores were less likely to respond [OR 0.59 (95% CI 0.50–0.69) per unit increase in HAQ] (Table 5). There was a significant association between current cigarette smoking and a lower response in patients receiving INF [OR 0.77 (95% CI 0.60–0.99)]. No association between smoking and outcome was seen in patients receiving ETA. Age, gender, disease duration and rheumatoid factor status were not significantly associated with response.

The baseline DAS28 score was not predictive of response. However, DAS28 is a composite score and we therefore investigated the predictive role of the individual components in predicting outcome. The results are shown in Table 6. In brief, the joint counts and patient global assessment were not predictive but a higher ESR quintile had a modest increase in risk of non-response. Given this greater impact of ESR alone over DAS28, we repeated the all predictor analysis (Table 5) substituting DAS28 with ESR. This made no difference to any of the other predictors.

We also explored the impact of disease duration by undertaking sub group analysis on those subjects of (a) <5 yrs and (b) <10 yrs duration to determine if the prediction model is improved in those subjects with potentially more reversible disease. Interestingly, there was very little difference though the effects were slightly more pronounced in the 'early' group.

TABLE 3. EULAR response after 6 months of therapy[a]

EULAR response	Overall (3223)	Etanercept (1413)	Infliximab (1810)
Good	584 (18.1)	245 (17.3)	339 (18.7)
Moderate	1602 (49.7)	727 (51.5)	875 (48.3)
None	1037 (32.2)	441 (31.2)	596 (32.9)
Remission	292 (8.6)	120 (8.0)	172 (9.0)

[a]Observed differences between etanercept and infliximab are not statistically significant.

TABLE 4. Table of baseline predictors among three response groups (in model only, $n = 2879$)

	Etanercept (1267)			Infliximab (1612)		
	EULAR response			EULAR response		
Variable	None (295)	Moderate (727)	Good (245)	None (398)	Moderate (875)	Good (339)
Demographic						
Age, mean (S.D.)	56 (12)	56 (12)	52 (13)	56 (12)	56 (12)	52 (12)
Female, *n* (%)	232 (78)	573 (79)	177 (72)	310 (78)	682 (78)	240 (71)
Current smokers, *n* (%)	52 (18)	160 (22)	42 (17)	101 (25)	177 (20)	69 (20)
Comorbidity, *n* (%)	171 (58)	453 (62)	119 (49)	227 (57)	502 (57)	170 (50)
Disease factors						
Disease duration, mean (S.D.)	14 (9)	14 (9)	15 (9)	14 (9)	14 (9)	13 (9)
Baseline DAS28, mean (S.D.)	6.5 (1.0)	6.9 (0.9)	6.4 (1.0)	6.6 (1.1)	6.8 (0.9)	6.4 (0.9)
Baseline HAQ score, mean (S.D.)	2.2 (0.5)	2.2 (0.5)	1.9 (0.6)	2.2 (0.5)	2.1 (0.5)	1.9 (0.6)
Rheumatoid factor positive, *n* (%)	202 (68)	541 (75)	162 (66)	289 (73)	641 (73)	236 (70)
Therapy						
Previous number of DMARDs, mean (S.D.)	4.5 (1.7)	4.5 (1.7)	4.2 (1.6)	4.2 (1.7)	4.2 (1.7)	3.9 (1.5)
Concurrent MTX, *n* (%)	55 (18)	200 (27)	101 (41)	326 (82)	756 (86)	300 (89)
Concurrent steroids, *n* (%)	163 (55)	352 (48)	113 (46)	195 (49)	442 (51)	155 (46)
NSAIDs, *n* (%)	176 (59)	472 (65)	177 (72)	248 (62)	575 (66)	255 (75)

TABLE 5. Predictors of higher EULAR Response at 6 months

	Etanercept		Infliximab	
Variable	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Demographic				
Age (per 10-yr increase)	0.98 (0.97–0.99)	0.99 (0.98–1.00)	0.98 (0.97–0.99)	0.99 (0.98–1.00)
Female	0.81 (0.63–1.05)	0.87 (0.66–1.15)	0.78 (0.63–0.98)	0.84 (0.66–1.07)
Current smokers (yes/no)	1.00 (0.77–1.31)	1.06 (0.80–1.41)	0.81 (0.64–1.01)	0.77 (0.60–0.99)
Comorbidity[a] (yes/no)	0.81 (0.65–1.00)	1.00 (0.78–1.27)	0.84 (0.70–1.02)	0.91 (0.74–1.13)
Disease factors				
Disease duration (per 10-yr increase)	1.00 (0.99–1.01)	1.01 (0.99–1.02)	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Baseline DAS28 (per unit)	0.94 (0.93–1.05)	1.11 (0.97–1.27)	0.90 (0.82–0.99)	0.95 (0.85–1.07)
Baseline HAQ Score (per unit)	0.47 (0.38–0.60)	0.51 (0.40–0.65)	0.57 (0.47–0.68)	0.66 (0.54–0.81)
Rheumatoid factor positive (yes/no)	0.97 (0.76–1.23)	1.02 (0.78–1.31)	0.91 (0.74–1.13)	0.95 (0.76–1.19)
Therapy				
Previous number of DMARDs (per drug)	0.92 (0.87–0.99)	0.97 (0.90–1.05)	0.94 (0.89–0.99)	0.96 (0.90–1.03)
Concurrent MTX	2.05 (1.61–2.61)	1.82 (1.38–2.40)	1.43 (1.09–1.87)	1.28 (0.95–1.73)
Concurrent steroids (yes/no)	0.79 (0.64–0.98)	0.94 (0.74–1.19)	0.93 (0.77–1.12)	0.99 (0.80–1.22)
NSAIDs	1.43 (1.14–1.79)	1.41 (1.10–1.79)	1.44 (0.18–1.76)	1.31 (1.05–1.63)

[a]Includes hypertension, ischaemic heart disease, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, renal disease, hepatic disease, depression, diabetes and thyroid disease.

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TABLE 6. Predictive role of individual DAS components

Variable	Etanercept		Infliximab	
	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
DAS components				
Swollen joint count (per joint)	1.00 (0.98–1.01)	1.00 (0.98–1.02)	1.00 (0.99–1.02)	1.01 (0.99–1.02)
Tender joint count (per joint)	1.00 (0.99–1.02)	1.00 (0.99–1.02)	0.99 (0.98–1.01)	0.99 (0.97–1.00)
ESR (per increasing quintiles)	0.86 (0.79–0.92)	0.86 (0.79–0.93)	0.86 (0.80–0.92)	0.86 (0.80–0.92)
Patient global assessment (per increasing quintiles)	0.97 (0.90–1.05)	0.97 (0.90–1.06)	0.98 (0.92–1.06)	1.02 (0.94–1.09)

INFLIXIMAB

NSAID + SMOKING + HAQ

Where:

NSAID = 1 if patient currently receiving NSAID
SMOKING = 1 if patient a current non-smoker
HAQ = 0 if HAQ score >2
= 1 if HAQ score between 1.0 and 2.0
= 2 if HAQ score ≤1.0

ETANERCEPT

NSAID + MTX + HAQ

Where:

NSAID = 1 if patient currently receiving NSAID
MTX = 1 if patient currently receiving MTX
HAQ = 0 if HAQ score >2
= 1 if HAQ score between 1.0 and 2.0
= 2 if HAQ score ≤1.0

FIG. 2. Formulae for predicting response.

Compared to the overall OR of response of 0.51 per unit increase in HAQ in the ETA group as a whole, in the subsets with (i) <5 yrs and (ii) <10 yrs, the OR were 0.59 and 0.55, respectively. For INF, against the whole group OR of 0.66, the 5- and 10-yr subgroup ORs were 0.44 and 0.71, respectively. There were no other predictors in the short disease (<5yrs) duration subgroup that improved the prediction of outcome.

There was an association between a better EULAR response and the concurrent use of NSAIDs for both therapies. The use of MTX was associated with a better response, although this only reached statistical significance in patients receiving ETA [OR 1.82 (95% CI 1.38–2.42)]. One problem in interpreting such findings in an observational study is that it is not random as to who receives these agents. Further, as increasingly anti-TNF-α agents are being co-prescribed with MTX, we explored the predictors of outcome within the MTX treated groups alone. HAQ (per unit increase) was still associated with a similar reduced risk of EULAR response: OR (95% CI) ETA 0.42 (0.27–0.68), INF 0.67 (0.53–0.84). There were no other predictors within the ETA group. In contrast, within the INF group, the higher (quintile) ESR was also modestly associated with a reduced EULAR response 0.89 (0.87–0.96).

To test the combined strength of these predictors, formulae were derived based on the strength of association between significant predictors and EULAR response in the logistic regression model. For INF these included: current NSAID use, current non-smoker and HAQ score. For ETA, this model included MTX use, NSAIDs, and HAQ score (Fig. 2). The proportion of good responders increased with increasing score for both drugs. For those with the highest score, 41% of INF and 40% of ETA patients were classified as good responders. More importantly <10% of those with a score of zero were classified as good responders (Table 7). Using an ordinal logistic regression model, for every one-point increase in score, patients receiving INF had a 50% better chance of being in a higher response category [OR 1.46 (95% CI 1.30–1.64)]. A similar result was found for ETA [OR 1.70 (95% CI 1.50–1.93)]. Essentially identical results were found when ESR was substituted for DAS28, with 41% of INF and 43% of ETA patients with the highest score classified as good responders, but <10% among those with the lowest score.

Predictors of remission

A similar model was used to identify the predictors of remission (defined as a 6 month DAS28 < 2.6) (Table 8). As for the EULAR response, a lower baseline HAQ score and the concurrent use of NSAIDs remained significant predictors of remission for both the anti-TNF-α therapies. In addition, females were significantly less likely to achieve remission compared with males following therapy with both the drugs [ETA: OR 0.61 (95% CI 0.38–0.94); INF: OR 0.60 (95% CI 0.40–0.89)]. There was also a correlation with a higher number of previous DMARDs and a lower remission rate [ETA: OR 0.83 (95% CI 0.71–0.97); INF: OR 0.85 (95% CI 0.75–0.98)]. Patients receiving the combination of ETA with MTX were more likely to achieve remission compared with those on ETA alone [OR 1.80 (95% CI 1.14–2.85)]. Although there was a trend towards a higher remission rate among patients receiving INF with MTX, this did not reach statistical significance [OR 1.24 (95% CI 0.68–2.27)]. Although comorbidity was identified as a negative predictor of remission in univariate analysis, it was not an independent predictor after adjusting for other baseline characteristics. Smoking was not a predictor of remission.

A similar prediction formula was generated to assess the cumulative strength of the various independent predictive factors (Fig. 3). For ETA, this model included gender, MTX, NSAIDs, HAQ score and DAS28, with a maximum possible score of 9. The model was similar for INF, but excluded MTX (maximum score 8). For those patients with a score <3, only 2.5% of ETA patients (8 of 310) and 4% of INF patients (14 of 358) were considered to be in remission at the end of 6 months (Table 9). However, for those few patients with a score >6 (67 ETA and 48 INF), 36 and 33%, respectively, were in remission at the end of the follow-up period. These scores correlated with a 70% increased chance of remission for every one-point increase in score [ETA: OR 1.71 (95% CI 1.50–1.93); INF: OR 1.65 (95% CI 1.47–1.87)].

Discussion

Therapy with anti-TNF-α drugs has revolutionized the management of RA. However, there still remains a proportion of patients who do not demonstrate any response. As these drugs have the potential of serious toxicity, the ability to identify those patients who will be most likely to respond could help optimize exposure

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TABLE 7. Combined strength of predictors in identifying response

	Infliximab				Etanercept			
		Response (%)				Response (%)		
Score	*n*	Good	Moderate	None	*n*	Good	Moderate	None
0	60	8	60	32	213	10	55	35
1	391	15	56	29	476	13	60	27
2	586	20	54	25	327	25	58	17
3	322	31	52	17	127	40	48	12
4	41	41	41	17	15	40	40	20

TABLE 8. Predictors of remission at 6 months

	Etanercept		Infliximab	
Variable	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Demographic				
Age (per 10-yr increase)	0.96 (0.95–0.98)	0.99 (0.97–1.00)	0.97 (0.96–0.98)	0.98 (0.97–1.00)
Female (yes/no)	0.58 (0.39–0.87)	0.61 (0.38–0.94)	0.55 (0.39–0.77)	0.60 (0.40–0.89)
Current smokers (yes/no)	0.73 (0.44–1.22)	0.63 (0.34–1.14)	1.17 (0.81–1.71)	1.03 (0.68–1.58)
Comorbidity[a] (yes/no)	0.55 (0.38–0.80)	0.96 (0.62–1.50)	0.70 (0.51–0.96)	0.88 (0.61–1.28)
Disease factors				
Disease duration (per 10-yr increase)	0.99 (0.96–1.00)	1.01 (0.98–1.03)	0.98 (0.97–1.00)	1.00 (0.98–1.03)
Baseline DAS28 (per unit)	0.49 (0.40–0.60)	0.57 (0.45–0.73)	0.61 (0.51–0.72)	0.65 (0.53–0.80)
Baseline HAQ score (per unit)	0.28 (0.19–0.42)	0.49 (0.32–0.79)	0.30 (0.22–0.43)	0.44 (0.30–0.64)
Rheumatoid factor positive (yes/no)	0.67 (0.46–1.00)	0.78 (0.49–1.24)	1.04 (0.73–1.48)	1.27 (0.85–1.90)
Therapy				
Previous number of DMARDs (per drug)	0.78 (0.69–0.88)	0.83 (0.71–0.97)	0.81 (0.73–0.90)	0.85 (0.75–0.98)
Concurrent MTX (yes/no)	2.75 (1.88–4.02)	1.80 (1.14–2.85)	1.62 (0.98–2.68)	1.24 (0.68–2.27)
Concurrent steroids (yes/no)	0.69 (0.47–1.01)	0.81 (0.52–1.25)	0.97 (0.71–1.33)	1.10 (0.76–1.59)
NSAIDs (yes/no)	1.96 (1.26–3.05)	1.79 (1.07–2.99)	2.25 (1.53–3.32)	1.93 (1.23–3.03)

[a]Includes hypertension, ischaemic heart disease, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, renal disease, hepatic disease, depression, diabetes and thyroid disease.

to these drugs and favourably alter their cost–benefit performance. In this large national cohort of RA patients receiving the TNF-α inhibitors INF and ETA, 68% of patients were classified as EULAR responders after 6 months of anti-TNF-α therapy. However, only 18% of patients achieved a good response and only 9% of patients were considered to be in remission. There were no overall differences in response between the two anti-TNF-α drugs. These results were similar to those presented in RCTs of these agents [1, 5, 6]. The results do reiterate, however, that approximately one-third of patients did not demonstrate an improvement, as defined using the EULAR criteria, despite up to 6 months of therapy.

Concurrent MTX, NSAIDs and a lower level of disability at the start of therapy were identified as predictors of response. In addition, current cigarette smoking was associated with a lower response rate among patients receiving INF. A higher number of previously failed DMARDs and female sex were also independently associated with a lower rate of remission. Despite the association between these factors and response, the cumulative strength of these individual factors in identifying responders was only moderate. Despite the absence of any positive predictors, as identified in our model, 8% of INF and 10% of ETA patients were still classified as good responders, suggesting other factors that may be important in determining the response. They are likely to be genetic and other constitutional factors, which may be linked to both disease activity and drug metabolism.

Certain methodological limitations must be considered while interpreting the results of this study. In this 'real world' study, the patients treated had long-standing disease and had failed several previous DMARDs. Assessing disease activity in such a group is problematic as joint swelling and tenderness may be a consequence of structural and, hence, irreversible damage. Similarly in late disease, the HAQ score is a marker for chronic radiologic damage [21]. There is a slowly increasing trend to use these agents earlier and it would be necessary to re-evaluate the role of predictors in such patients. However, even among this severe cohort, patients were less likely to respond if they had higher baseline HAQ scores. Similar results have been found when predicting the response to other non-biological DMARDs, including MTX and leflunomide [22, 23]. Therefore, in these patients with long-standing RA, the HAQ score may also be a reflection of irreversible disease.

We used a cut-off for remission of 2.6, whereas others have used more stringent cut-offs such as 2.32 [24] and 2.4 [25]. We repeated the analysis using these more stringent cut-offs and though there was a smaller prevalence of remission (6.8 and 7.5 *vs* 8.6% observed with 2.6), there were no differences in the predictors.

The findings in this analysis support the combined use of anti-TNF-α therapy with MTX. Even after adjusting for other potential predictors, patients receiving either ETA or INF with MTX experienced a better response compared with those not receiving MTX. There was an interesting finding of a better outcome among the patients receiving NSAIDs. A similar beneficial effect of NSAID therapy had been demonstrated in patients receiving MTX [26]. The reason for this is not clear. Although there is evidence that NSAIDs may improve inflammation in RA [27], it is unlikely that this explains these findings, as all

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INFLIXIMAB

MALE + HAQ + NSAID + DAS28 + PREVDM

Where:
MALE = 1 if patient is a male
NSAID = 1 if patient currently receiving NSAID
MTX = 1 if patient currently receiving MTX
HAQ = 0 if HAQ score >2
= 1 if HAQ score between 1.0 and 2.0
= 2 if HAQ score ≤1.0
DAS = 0 if DAS28 score >7.2
= 1 if DAS28 score between 6.2 and 7.2
= 2 if DAS28 score ≤6.2
PREVDM = 0 if >5 previous DMARDs
=1 if 4 or 5 previous DMARDs
=2 if 3 or fewer previous DMARDs

Total possible score: 8

ETANERCEPT

MALE + HAQ + MTX + NSAID + DAS28 + PREVDM

Where:

MALE = 1 if patient is a male
NSAID = 1 if patient currently receiving NSAID
MTX = 1 if patient currently receiving MTX
HAQ = 0 if HAQ score >2
= 1 if HAQ score between 1.0 and 2.0
= 2 if HAQ score ≤1.0
DAS = 0 if DAS28 score >7.2
= 1 if DAS28 score between 6.2 and 7.2
= 2 if DAS28 score ≤6.2
PREVDM = 0 if >5 previous DMARDs
=1 if 4 or 5 previous DMARDs
=2 if 3 or fewer previous DMARDs

FIG. 3. Formulae for predicting remission.

TABLE 9. Combined strength of predictors in identifying remission

	Infliximab		Etanercept	
Score	*n*	Remission (%)	*n*	Remission (%)
0–2	358	3.9	310	2.5
3–4	622	6.7	487	3.3
5–6	378	20.1	294	13.6
>6	48	33.3	67	35.8

of these patients had been established on the medication prior to the initiation of biological therapy. However, it is possible that NSAIDs may potentiate the effects of anti-TNF-α therapies, either through enzymatic induction or through other pathways. The more likely possibility is that NSAIDs themselves have no effect on response, but serve as a marker for another important factor. One possibility is the absence of comorbidity, as NSAIDs may be avoided in patients with hypertension, renal, liver and cardiac disease, although the strength of NSAIDs persisted even after adjusting for the presence of these other comorbidities. There is also the possibility that the use of NSAIDs is a marker for current inflammatory symptoms (i.e. a reversible component of patient symptoms). However, the results of this study cannot justify the initiation of NSAIDs in patients considering anti-TNF-α therapy.

Smoking was also found to be a negative predictor of response to INF but not of ETA and was only significant on multivariate analysis. There is no biologically plausible reason why the two drugs should differ and this effect may be a chance finding, given the large number of variables examined. However, nicotine or other factors related to cigarette smoking may interfere with the absorption or metabolism of certain drugs. Rahman *et al.* [28] found that cigarette smoking resulted in a decreased efficacy of hydroxychloroquine in patients with cutaneous lupus. Cigarette smoking is a well-recognized risk factor for the development of RA [29, 30]. It has also been associated with more severe diseases, including higher levels of disability [31] and extra-articular manifestations, particularly nodules [32, 33]. It is also possible that smoking might be related to an increased rate of discontinuation for adverse events. We addressed this and found an identical adverse event rate leading to withdrawal (10%) in both smokers and non-smokers.

The finding of a lower remission rate among females is in keeping with other studies analysing response to non-biological DMARDs [21, 26]. Previous studies have also found an association between a higher number of failed DMARDs and poor response to non-biological DMARDs [22, 34–36]. It is possible that those patients who have failed many DMARDs represent a subgroup of RA patients with highly resistant disease. These patients may also have genetic differences that affect their drug metabolism. It is also possible that previous DMARDs may alter drug kinetics or enzymatic pathways of drug metabolism, rendering patients less responsive to future DMARDs.

In the current funding climate within the UK, at least during the period of recruitment to this study, the use of biological agents has been restricted to those who are perhaps less likely to respond. This is also true for the majority of European countries (several personal communications). Although we showed that restricting the analysis to the subset with shorter duration disease (5 or 10 years) did not alter the findings, this may be a consequence of equal 'biased' selection of severe non-responding 'early' patients. If these agents become more widely used at an earlier stage, then it will be necessary to repeat analyses such as this.

Conclusions

In this observational study of response to anti-TNF-α therapies, certain factors emerged as independent predictors of response. A high level of baseline disability was a strong predictor of EULAR non-response. The concurrent use of MTX was a strong predictor of response, particularly in those patients receiving ETA. In addition, females were less likely to achieve remission within the first 6 months of therapy. In the UK, as in Europe (reported experience of representatives from several European Registries of anti-TNF-α drug use at meeting in Berlin, 2004), anti-TNF-α agents have been used, at least until recently, in patients with severe, long-standing disease. In such patients, it is not easy to predict who will achieve a good response. Nevertheless, the response to biological drugs is unlikely to be a random effect and further work is needed to identify the genetic and environmental factors that may determine the response. It would be important to undertake such work separately in those patients with early as well as with late and otherwise persistently active disease.

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