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Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity

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Objectives. Anti-TNF therapy has improved outcomes for patients with highly active RA. Less is known about its effectiveness in patients with lower disease activity. The aim of this analysis is to compare the response to anti-TNF therapy between RA patients with high (DAS28 > 5.1) and moderate (DAS28 > 3.2–5.1) disease activity.

Methods. A total of 4687 anti-TNF and 344 DMARD patients with high disease activity despite treatment with two standard DMARDs (including MTX) and 224 anti-TNF- and 300 DMARD-treated patients with moderate disease activity were selected from the British Society For Rheumatology Biologics Register. Mean change in HAQ over the first 12 months of enrolment was compared first between anti-TNF-treated and untreated patients in each DAS28 group, and then between anti-TNF-treated patients in the moderate and high DAS28 groups, using doubly robust estimates, adjusting for age, gender, disease duration, baseline HAQ and DAS28 score, number of previous DMARDs and steroid use.

Results. Compared with anti-TNF-untreated patients within each DAS group, treated patients were younger, had higher DAS28 and HAQ and had failed a higher number of previous DMARDs. The mean adjusted change in HAQ over 12 months was similar in anti-TNF-treated patients with moderate and high disease activity at baseline: moderate −0.26 (95% CI −0.35, −0.16), high −0.28 (95% CI −0.34, −0.23) and mean difference −0.03 (95% CI −0.14, 0.08).

Conclusions. Improvement in HAQ score 12 months after start of anti-TNF therapy was not dependent on baseline DAS28 scores, suggesting that substantial benefits may also be gained by treating those with moderately active disease despite standard DMARD therapy.

Key words: Rheumatoid arthritis, Anti-TNF, DMARDs, Disease activity, Disability, Treatment outcome.

Introduction

The anti-TNF therapies, developed against the background of an increasing understanding of the pathogenesis of RA, represent a tremendous advance in the management of RA. Their use has added to the confidence of healthcare professionals and patients that disease previously resistant to conventional DMARDs can usually be satisfactorily controlled, and remission of disease is an increasingly realistic aim. However, these therapies are expensive in comparison with conventional DMARDs and, in countries with socialized healthcare, their unrestricted use would be unaffordable. In the UK, eligibility criteria for the use of these agents have been issued by the British Society for Rheumatology and the National Institute for Health and Clinical Excellence (NICE) [1]. The current guidelines for initiation of anti-TNF agents in patients with RA suggest that a patient should have a 28-joint count disease activity score (DAS28) >5.1 [2] on two occasions at least 1 month apart despite adequate previous treatment with at least two DMARDs, one of which should have been MTX. Adequate treatment is defined as a therapeutic course of at least 6 months unless side effects are experienced.

In recent years, there has been a shift towards the early aggressive treatment of RA, with a goal of low disease activity. The Tight Control of Rheumatoid Arthritis (TICORA) study found that early aggressive therapy in RA, with a goal DAS <2.4, resulted in better clinical and radiographic outcomes [3]. Similarly, the recent BeSt (a Dutch acronym for Behandel-Strategiee, or 'treatment strategies') study, which randomized patients with early RA to one of the four treatment strategies, found the best outcomes in those regimes with a rapid reduction and maintenance of disease activity below a DAS of 2.4 [4]. Follow-up from this same study found that the efficacy of subsequent standard DMARD treatment after initial failure with MTX (defined as failure to reduce DAS <2.4 or toxicity) was limited, with many patients subsequently requiring anti-TNF therapy to bring the disease under control [5]. Control of disease activity to very low levels in RA has also been shown to significantly reduce work disability in patients with early RA [6].

The use of standard DMARD therapy alone will result in a proportion of patients with ongoing moderate disease activity. There are, however, limited data on the effectiveness of anti-TNF therapies in patients with moderate disease activity, compared with those with high disease activity. A number of studies [7–10] have found that patients who start anti-TNF therapy with lower DAS28 scores are more likely to achieve disease remission, defined using a DAS28 < 2.6, but less likely to reach a 50 or 70% improvement in disease activity, defined using the ACR response criteria [11]. The results of these studies are intuitive as it is likely easier to reach a very low DAS28 score if one starts with lower disease activity, whereas those with high DAS28 are more likely to experience larger percentage of improvements due to regression to the mean.

Many health economic models in RA are based on the HAQ, a widely used patient reported outcome measure of physical function [12]. HAQ scores are also important predictors of other clinical outcomes, such as future work disability [13] and mortality [14]. There are no previous studies specifically looking at the influence of anti-TNF therapy on HAQ in RA patients with moderate disease activity. Therefore, using data from patients enrolled in the British Society for Rheumatology Biologics Register (BSRBR), this analysis compares the response to anti-TNF therapy, defined using absolute change in HAQ score over a 12-month period, first between anti-TNF-treated and -untreated patients

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with moderate disease activity despite previous treatment with at least two standard DMARDs, including MTX, and second, between anti-TNF-treated patients with moderate and high disease activity at the start of therapy.

Methods

Patient population

Patients for this study were selected from the BSRBR. This study, established in October 2001, has been systematically following patients from start of anti-TNF therapies for RA. Details of this study have been published elsewhere [15]. A parallel comparison arm of patients receiving DMARD therapy is also being recruited. The study was approved by the North West Multicentre Research Ethics Committee, and all subjects gave their written consent for participation.

Baseline data collection

Anti-TNF cohort. Patients with no previous exposure to biologic agents who were starting one of the three available anti-TNF agents (etanercept, infliximab or adalimumab) in any hospital throughout the UK were eligible to be registered at the start of anti-TNF therapy. Their rheumatology consultant or clinical nurse specialist completed a baseline form that includes demographic details, diagnosis, current and past anti-rheumatic therapy and DAS28 at the time the first anti-TNF therapy was started. In addition, the patient was asked to complete the UK version of the HAQ [16]. All data were collected centrally at the University of Manchester.

DMARD cohort. Twenty-five hospitals across the UK were designated as control centres (see Appendix 1). Control patients were selected if they had RA, were receiving a DMARD, had no history of exposure to biologic therapies and were felt to have active disease (a guide DAS28 of at least 4.2 was provided although patients may have had lesser disease activity). Data collection was identical to that of the anti-TNF cohort with the exception of the HAQ, which was posted directly to the patient's home for completion and return by post.

Follow-up data collection. Follow-up data collection is identical for both cohorts and is ongoing for the larger study. On a 6-monthly basis for 3 years and then annually thereafter, hospitals are contacted for updated information on disease activity, changes to anti-rheumatic therapy and the development of any adverse events. All patients (anti-TNF and DMARD) are posted a HAQ to their homes for completion and return to the University of Manchester by post.

Data analysis. The primary outcome of this analysis was change in HAQ score over the first 12 months of anti-TNF therapy or the first 12 months of observation (for DMARD controls). Patients in the anti-TNF cohort were included if they had been registered within 90 days of starting their first anti-TNF therapy, had failed at least two DMARDs, had a DAS28 recorded at baseline and had completed a baseline and 12-month HAQ. The 90-day cut-off was chosen to ensure that the 12-month follow-up questionnaires were completed as close as possible to 1 year after starting the anti-TNF therapy, yet allow time for baseline forms to be completed by the recruiting hospitals. Patients were selected from the DMARD control cohort for analysis if they had received therapy with at least two DMARDs, one of which must have been MTX. For patients in the control group who had only ever received two DMARDs, they must have been receiving the second DMARD for at least 6 months. Similarly, patients needed to have a DAS28 recorded at baseline and have completed a baseline and 12-month HAQ. All patients were subsequently divided into two groups based on baseline DAS28 score (moderate: >3.2–5.1 and high: >5.1). Baseline characteristics were compared using non-parametric descriptive statistics. Response (change in HAQ over 12 months) was modelled using doubly robust estimation. This technique, developed by Bang and Robins [17], aims to combine the advantages of regression modelling and inverse probability of treatment weighting (IPTW) [18]. Regression modelling fits a model for the outcome with treatment as a predictor, and adjusts for imbalances in covariates between the treated and untreated by including these covariates in the outcome model. IPTW modelling uses the covariates in a logistic regression model to predict the probability of receiving treatment, and by weighting by the inverse of the probability of receiving treatment, produces a pseudopopulation in which the covariates are no longer confounders. Both of these methods should produce unbiased estimates if the assumptions of the methods are met, namely that the outcome model is correctly specified for regression modelling and that the probability of treatment is correctly specified for the IPTW model. The doubly robust model will produce an unbiased estimate if either of the two models is specified correctly. The analysis was performed using the Stata command *dr* [19]. The following baseline covariates were entered into the models: age, gender, disease duration, baseline HAQ, baseline DAS28, previous number of DMARDs and current use of steroids (yes/no). Results are presented as the adjusted mean change in HAQ with 95% CIs. The response was first compared between anti-TNF and DMARD patients within each DAS28 group, and then the response was compared between anti-TNF patients with moderate and high disease activity.

Results

Study population

Until 13 December 2007, 8448 anti-TNF patients had started their first anti-TNF within 90 days of registration, had failed two previous DMARDs, including MTX, and had a baseline HAQ and DAS28 recorded. Of these, 6935 patients had reached 12 months of follow-up and 4922 had completed a 12-month HAQ (71%): 224 (4.6%) had moderate disease and 4687 (95.2%) had high disease activity at baseline, in keeping with national guidelines. Eleven patients had a DAS28 $\leqslant 3.2$ recorded at the start of therapy and were excluded from the analysis.

To the same date, 1675 DMARD control patients had been registered with the BSRBR who had received treatment with at least two DMARDs, including MTX. Of these, a baseline HAQ and DAS28 was available for 1300 (78%). A total of 1010 patients had reached 12 months of follow-up and 720 had completed a 12-month HAQ (71%): 300 (42%) had moderate disease and 344 (47%) had a DAS28 >5.1. The remaining patients had low disease activity at baseline and were excluded from the analysis.

Baseline characteristics

Baseline characteristics are summarized in Table 1. All groups were similar with respect to gender and disease duration, but patients in the DMARD cohort tended to be slightly older than patients who were started on anti-TNF (63 *vs* 57, $P < 0.001$ in the moderate DAS28 group and 60 *vs* 58, $P < 0.001$ in the high DAS28 group). Patients who received anti-TNF therapy tended towards higher disease activity, demonstrated with higher swollen and tender joint counts. ESRs were similar between anti-TNF-treated and -untreated cohorts in both DAS28 groups, but there was a significantly higher proportion of anti-TNF-treated patients who were receiving corticosteroids. Similarly, patients who had received anti-TNF, regardless of baseline DAS28, had failed a higher number of previous DMARDs.

TABLE 1. Baseline characteristics in patients according to baseline DAS28 group and treatment group

Baseline DAS28 group	>3.2–5.1			>5.1		
Treatment group	DMARD	Anti-TNF	*P*-value	DMARD	Anti-TNF	*P*-value
n	300	224		344	4687	
Age, years	63 (56–69)	57 (49–64)	<0.001	60 (54–69)	58 (50–65)	<0.001
Female, *n* (%)	229 (76)	162 (72)	0.297	276 (80)	3612 (77)	0.176
Disease duration, years	13 (7–21)	12 (7–21)	0.423	11 (5–21)	11 (6–19)	0.876
DAS28 score	4.33 (3.84–4.68)	4.74 (4.29–4.96)	<0.001	5.93 (5.49–6.61)	6.65 (6.01–7.31)	<0.001
28 swollen joint count	3 (1–5)	5 (3–9)	<0.001	7 (4–10)	11 (7–16)	<0.001
28 tender joint count	4 (2–6)	5 (2–8)	0.002	12 (8–18)	16 (11–22)	<0.001
ESR, mm/h	21 (12–36)	21 (12–32)	0.363	39 (25–57)	42 (26–65)	0.048
CRP, mg/l	16 (8–33)	19 (9–39)	0.287	25 (12–46)	34 (17–66)	0.003
Patient global assessment (100-mm VAS)	46 (27–60)	50 (32–70)	0.010	70 (50–80)	75 (64–87)	<0.001
Receiving oral steroids, *n* (%)	73 (24)	114 (51)	<0.001	86 (25)	2147 (46)	<0.001
No. of DMARDs (previous)	3 (2–4)	4 (3–5)	<0.001	3 (3–4)	4 (3–5)	0.001

Values are given as median (interquartile range) unless otherwise specified.

TABLE 2. HAQ score at baseline and 12 months

Baseline DAS28	>3.2–5.1		>5.1	
Treatment group	DMARD	Anti-TNF	DMARD	Anti-TNF
n	300	224	344	4687
HAQ baseline, mean ± S.D.	1.43 ± 0.76	1.78 ± 0.61	1.87 ± 0.63	2.05 ± 0.55
HAQ 12 months, mean ± S.D.	1.45 ± 0.78	1.51 ± 0.75	1.85 ± 0.63	1.71 ± 0.72
Patients with >0.22 improvement in HAQ score at 12 months, *n* (%)	72 (24)	119 (53)	93 (27)	2725 (58)
Mean change in HAQ, 95% CI	0.03 (−0.02, 0.07)	−0.27 (−0.34, −0.21)	−0.01 (−0.06, 0.03)	−0.35 (−0.36, −0.33)
Unadjusted mean change in HAQ (95% CI) (anti-TNF *vs* DMARDs)	Reference	−0.30 (−0.38, −0.22)	Reference	−0.33 (−0.40, −0.29)
Unadjusted mean difference in HAQ change between moderate and high DAS, 95% CI (anti-TNF only)		Reference		−0.03 (−0.12, 0.06)
Adjusted mean change in HAQ (95% CI) (anti-TNF *vs* DMARDs)	Reference	−0.26 (−0.35, −0.16)	Reference	−0.28 (−0.34, −0.23)
Adjusted mean difference in HAQ change between moderate and high DAS (95% CI) (anti-TNF only)		Reference		−0.03 (− 0.14, 0.08)

Change in HAQ score during first 12 months of observation

For both the DMARD and the anti-TNF cohorts, the baseline HAQ score was higher in those patients in the high DAS28 group (Table 2). Within each DAS28 group, the HAQ score was significantly higher in those patients who received anti-TNF therapy. However, treatment with anti-TNF therapy resulted in similar reductions in HAQ score in both DAS28 groups when compared with the untreated group [adjusted mean improvement −0.26 (95% CI −0.35, −0.16) in the moderate DAS28 group and −0.28 (95% CI −0.34, −0.23) in the high DAS28 group]. The difference in improvement in HAQ score between the moderate and high DAS28 anti-TNF-treated groups was not statistically significant [mean difference −0.03 (95% CI −0.14, 0.08)]. In addition, a similar proportion of patients in each anti-TNF-treated group had an improvement in HAQ score in excess of the minimally clinically important difference (MCID) of 0.22 U [20] (moderate DAS28 group: 53% and high DAS28 group: 58%, $P = 0.14$) (Table 2). The main driver for the difference in improvement between anti-TNF and DMARD controls in both DAS28 groups appeared to be the improvement gained in the anti-TNF group, with no progression or improvement in HAQ seen over 12 months in the DMARD control group in either the moderate or the high DAS28 group.

Concern has been raised that the DAS28 may not adequately reflect disease activity in certain patients and can be raised by a high number of tender joints and high patient global assessment in the absence of swollen joints. There were differences in the proportion of patients with less than three swollen joints in the four treatment groups (moderate DAS28: DMARD 40%, anti-TNF 25%, $P < 0.001$; high DAS28: DMARD 11%, anti-TNF 4%, $P < 0.001$). However, total number of swollen joints was not found to be associated with change in HAQ score in the regression model for either the moderate DAS28 group [β-coefficient −0.004 per joint (95% CI −0.013, 0.006)] or the high DAS28 group [β-coefficient −0.0004 per joint (95% CI −0.003, 0.002)].

Discussion

The results of this study have shown that treatment with anti-TNF therapy is effective both in patients with high and moderate disease activity. In addition, the magnitude of improvement in both of these groups is similar, with a mean improvement in HAQ score in excess of a minimally clinically important improvement (>0.22) [20].

This study is not a clinical trial but rather an observational study of real-world treatment response among patients in the UK, and therefore, does have some limitations which must be considered. As treatment was not assigned randomly to patients, statistical models were used to account for differences in baseline disease severity. These are dependent on the covariates entered into the model and therefore, we cannot exclude the effects of unmeasured confounding. Missing data may also have influenced the results. Up to 25% of the patients did not return their HAQ score at 1 year. In general, in both treated and untreated patients, those who returned their forms were slightly older (DMARD: 61 *vs* 59 years, $P = 0.05$; anti-TNF: 57 *vs* 55 years, $P = 0.001$) and had

slightly longer disease duration (DMARD: 9.9 *vs* 9.5 years, $P = 0.008$; anti-TNF: 13.6 *vs* 12.7, $P = 0.001$). Among untreated patients, those who did not return their forms tended towards high HAQ scores at baseline (1.6 *vs* 1.4, $P = 0.005$) although in the treated group, there was no association between baseline HAQ score and form return rate (2.05 in both groups). Therefore, there is a possibility that we have over- or underestimated the improvement in HAQ in either DAS28 groups.

In the UK, there are national guidelines which restrict the use of anti-TNF therapies to those patients with a high DAS28. Despite these guidelines, there was a group of patients who received these therapies with a DAS28 < 5.1. It is possible that these patients are fundamentally different from patients who receive these agents in countries without these restrictions, meaning the results may not be generalizable to a wider population. There is also a possibility that these patients did have a high DAS28 score at one point prior to treatment with anti-TNF, but while waiting for therapy to begin, patients experienced a drop in their DAS28 due to either natural variation in disease activity or another intervention (e.g. i.m. steroid injection). A review of the notes of patients from two centres suggests that i.m. steroids had been administered a few weeks before the assessment in up to 50% of the patients. However, a generally lower HAQ score at the start of therapy in patients with moderate disease activity compared with those patients with high DAS28 suggests that these patients did have lower disease activity. They were also more likely to be already receiving oral steroids and to have failed a higher number of previous DMARDs. Therefore, the physician may have felt that anti-TNF therapy was the next best therapy for these patients, regardless of their DAS28.

Similarly, we observed a cohort of patients that should have been eligible for anti-TNF therapies according to DAS28 who did not receive these therapies. Again, a long wait for treatment in some areas (at times many months) may have resulted in these patients being registered in the control arm of this study, although over the course of the first year, only two patients in the moderate DAS28 group and 11 patients in the high DAS28 group received anti-TNF therapy. Exclusion of these patients from the analysis did not alter the results. There may also have been other unmeasured factors, such as general frailty or other medical contraindications of treatment, which were not recorded by the register which may also have influenced the physician's choice of treatment.

The patients in this study were analysed according to baseline DAS28. However, the DAS28 itself is not without its limitations and the treating physicians may have made treatment decisions independent of DAS28 in certain patients. The DAS28 has a strong weighting towards tender joint count and patient global assessment, two relatively subjective measures of disease activity. Indeed, studies have found that patients without inflammatory arthritis but significant FM can also score high on the DAS28 [21]. Therefore, certain patients with high disease activity may not have, in the physician's opinion, had disease activity high enough to warrant anti-TNF therapy. The DAS28 also excludes certain joints, including the hips, ankles and feet, which may have been important factors in deciding on therapy in individual cases. Therefore, the DAS28 may not capture the full degree of disease activity in the patient.

Despite these limitations, the observed improvements in HAQ score were in the same range as those seen in randomized clinical trials of anti-TNF therapies for MTX-resistant disease, which ranged from an improvement of 0.15 up to 0.6 U [22–27] with the vast majority showing a net improvement in the range of 0.3 when placebo response was considered. Patients in our DMARD group should be considered as routine care and no specific direction was given to try and reduce the disease activity below a certain level. It is interesting to note that within this group, the mean HAQ score did not change and only 25% of this group experienced an improvement in excess of the MCID in HAQ score, compared with >50% in the treated groups.

In conclusion, the results of this study indicate that the effectiveness of anti-TNF therapy in improving the level of disability among patients with severe DMARD-resistant RA appears to be independent of baseline DAS28 score. Therefore, patients with ongoing moderate disease activity despite treatment with DMARDs may also benefit from biologic therapy. The results of this study also indicate that anti-TNF therapy for those with moderate DAS28 may be just as cost effective as treatment of those with higher DAS28 scores, especially when assessed in health economic models which are based on changes in HAQ [12].

Rheumatology key messages

- Anti-TNF agents significantly improve disability in patients with persistent disease activity despite standard DMARDs.
- The influence of anti-TNF therapy on disability is independent of baseline disease activity level.

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Appendix

The BSRBR Control Centre Consortium consists of the following institutions (all in the UK): Antrim Area Hospital, Antrim (Dr Nicola Maiden); Cannock Chase Hospital, Cannock Chase (Dr Tom Price); Christchurch Hospital, Christchurch (Dr Neil Hopkinson); Derbyshire Royal Infirmary, Derby (Dr Sheila O'Reilly); Dewsbury and District Hospital, Dewsbury (Dr Lesley Hordon); Freeman Hospital, Newcastle-upon-Tyne (Dr Ian Griffiths); Gartnavel General Hospital, Glasgow (Dr Duncan Porter); Glasgow Royal Infirmary, Glasgow (Prof. Hilary Capell); Haywood Hospital, Stoke-on-Trent (Dr Andy Hassell); Hope Hospital, Salford (Dr Romela Benitha); King's College Hospital, London (Dr Ernest Choy); Kings Mill Centre, Sutton-In Ashfield (Dr David Walsh); Leeds General Infirmary, Leeds (Prof. Paul Emery); Macclesfield District General Hospital, Macclesfield (Dr Susan Knight); Manchester Royal Infirmary, Manchester (Dr Ian Bruce); Musgrave Park Hospital, Belfast (Dr Allister Taggart); Norfolk and Norwich University Hospital, Norwich (Prof. David Scott); Poole General Hospital, Poole (Dr Paul Thompson); Queen Alexandra Hospital, Portsmouth (Dr Fiona McCrae); Royal Glamorgan Hospital, Glamorgan (Dr Rhian Goodfellow); Russells Hall Hospital, Dudley (Prof. George Kitas); Selly Oak Hospital, Selly Oak (Dr Ronald Jubb); St Helens Hospital, St Helens (Dr Rikki Abernethy); Weston General Hospital, Weston-super-Mare (Dr Shane Clarke/Dr Sandra Green); Withington Hospital, Manchester (Dr Paul Sanders); Withybush General Hospital, Haverfordwest (Dr Amanda Coulson); North Manchester General Hospital (Dr Bev Harrison); Royal Lancaster Infirmary (Dr Marwan Bukhari); and The Royal Oldham Hospital (Dr Peter Klimiuk).