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Original article

Changes in disease characteristics and response rates among patients in the United Kingdom starting anti-tumour necrosis factor therapy for rheumatoid arthritis between 2001 and 2008

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Abstract

Objectives. Anti-TNF therapy has significantly improved outcomes for patients with severe RA. In the UK, changing financial restrictions and increasing experience with their use may have resulted in changes to the way physicians use anti-TNF therapies. The aim of this analysis was to examine changes in disease characteristics and response rates among patients starting anti-TNF therapy for RA over an 8-year period.

Methods. A total of 11 216 RA patients registered between 2001 and 2008 with the British Society for Rheumatology Biologics Register were included and stratified according to year of first anti-TNF prescription. Baseline characteristics and treatment response were compared year on year using logistic and linear regression models.

Results. Mean RA disease activity and severity of new anti-TNF-treated patients decreased between 2001 and 2008. The mean disease duration remained high (11 years in 2008) although the proportion of patients having disease duration <5 years increased significantly (2001: 9%; 2008: 29%; $P < 0.001$). The majority of patients had failed three DMARDs on average before the first anti-TNF prescription. There was an increase in both the proportion of EULAR good responders at 1 year (2001: 18%; 2008: 30%; $P < 0.001$) and in the number of patients achieving remission (2001: 8%; 2008: 17%; $P < 0.001$). Drug survival remained relatively stable over the study years.

Conclusions. There is a significant trend towards earlier use of anti-TNF therapies in patients with less severe disease, although the mean disease duration at first treatment remains high. This has correlated with improvements in outcome. These results support the earlier use of anti-TNF therapies in RA.

Key words: Rheumatoid arthritis, Anti-TNF therapy, Prescription pattern, Treatment response, Treatment outcome, Remission.

CLINICAL SCIENCE

Introduction

The anti-TNF agents have significantly improved outcomes for patients with severe RA. Since their licence in the late 1990s, the utility and place of anti-TNF therapies in the treatment of RA has been expanding, with increasing data to support their earlier use [1–4]. Further data has also supported the benefits of combining these agents with MTX and other DMARDS, both in those naïve to DMARD treatment [4, 5] and in those resistant to MTX [6].

There are some data to suggest that these published observations are translating into clinical practice. A number of studies outside of the UK have demonstrated that the prescription of anti-TNF therapies in both early and established RA is increasing [7–11]. A US study by Yazici *et al*. [9] also demonstrated that co-prescription with MTX increased over the period from 1999 to 2005. However, whether these changes in use have translated into better outcomes in routine clinical practice is less

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clear. Analysis of the Danish Biologics Registry (DANBIO) data set found that baseline DASs decreased over a 5-year period [12]. The 12-month EULAR and DAS-28 responses over the same period of observation also significantly improved. However, data on whether anti-TNF therapies were being used earlier in disease over this same period were not presented. The aim of this study was to explore the secular patterns of anti-TNF prescribing in the UK over an 8-year period (2001–08) including changes in the baseline characteristics of the patients and the association with treatment response, improvements in disability and treatment survival.

Patients and methods

Patients included this study were participants in the British Society for Rheumatology Biologics Register (BSRBR) [13]. The BSRBR aimed to recruit 4000 patients with RA starting each of the three currently available (2009) anti-TNF therapies: etanercept, infliximab and adalimumab. Recruitment to the etanercept and infliximab cohort began in October 2001 and adalimumab recruitment began in 2003. The target of 4000 patients was reached for etanercept in May 2005, infliximab in 2007 and adalimumab at the end of 2008. The prescription of anti-TNF therapy in the UK is according to the national guidelines [14] and in England and Wales, governed by the National Institute of Clinical Excellence (NICE) [15]. Since their approval in the UK, these treatments have been reserved for patients with a 28-joint count DAS-28 [16] >5.1 despite treatment with at least two standard DMARDs (one of which must include MTX).

At treatment start, details including diagnosis, disease activity, new biologic therapy, past and current anti-rheumatic therapies and information on other comorbidities were collected from the treating physician. The patient also completed an HAQ adapted for British use [17]. Follow-up is completed at 6-month intervals for the first 3 years and annually thereafter. At each follow-up, the physician completes a questionnaire detailing any changes in anti-rheumatic therapy, including dates and reasons for any changes and current disease activity. For the first 3 years of the study, an HAQ form is mailed every 6 months to the patients' homes to complete and return. Response rates have been very good, with $>90\%$ of all hospital follow-up forms returned and $\sim 75\%$ of patient questionnaires returned. The study received ethical approval from the North West UK Research Ethics Committee (MREC 00/8/53) and all patients provided written informed consent.

This analysis was limited to biologic-naïve patients starting their first anti-TNF within 6 months of registration with the BSRBR. Patients were divided into cohorts based on the calendar year of treatment start (2001–08). All anti-TNF therapies were analysed together. Differences in baseline characteristics across the years were compared using linear and logistic regression models, with the characteristic as the outcome and year as a covariate.

Improvements in disease activity and disability were compared in three ways. First, the absolute mean change in DAS-28 and HAQ score were compared across the study years using linear regression models. Secondly, the proportion of EULAR responders [18] (moderate and good responders *vs* non-responders) and the proportion of patients in DAS-28 remission [19] (defined as DAS-28 <2.6) were compared using a logistic regression model. Finally, the proportions of patients with a EULAR non-response, moderate response or good response in each year were compared using an ordinal logistic regression model, which models the odds of being in a higher response category for each consecutive calendar year. Anti-TNF survival at 1 and 2 years was examined for each consecutive treatment year using Kaplan–Meier survival curves and compared across the years using Cox proportional hazards models. All outcome analyses were adjusted additionally for choice of anti-TNF agent.

Results

Until 30 June 2009, 11 216 patients with RA starting their first anti-TNF therapy within 6 months of study registration had been recruited to the BSRBR from 257 hospitals across the UK (3940 etanercept, 3316 infliximab and 3960 adalimumab). The proportion of patients starting each of the three drugs differed over the course of the study relating to changes in recruiting patterns within the BSRBR (Table 1).

Between 2001 and 2008, there was a significant trend towards the use of these drugs in patients who were older and with shorter disease duration (Table 1). Only 13% of the cohort recruited in 2002 had disease duration <5 years. This increased to 29% in 2008. However, in 2008, the overall mean disease duration was still high at 11 years, with only 5% of patients receiving their first biologic within 2 years of disease onset. Despite NICE guidance allowing the use of anti-TNF after two failed DMARDs (including MTX), the mean number of failed DMARDs before starting anti-TNF remained at three in 2008, with only 30% of patients receiving their anti-TNF after only two failed DMARDs. The proportion of patients with at least one comorbid condition remained constant at $\sim 60\%$ across the years.

The use of concurrent DMARDs remained unchanged over the study period in patients starting infliximab, with $\sim 85\%$ of patients receiving MTX (Table 2). The proportion of patients receiving concurrent DMARDs with either etanercept or adalimumab increased with 44% of patients starting etanercept in combination with MTX in 2005 and 62% starting adalimumab in combination with MTX in 2008. This compared with only 21% of patients starting etanercept in 2002 and 37% of patients starting adalimumab in 2003. The proportion of patients receiving oral corticosteroids decreased over the study years.

The DAS-28 was available for 11 119 (99%) patients at baseline, 10 291 (92%) patients at 6 months and 8646 (77%) patients at 1 year. HAQ scores were available for 10 672 (95%) patients at baseline, 8155 (72%) patients at 6 months and 7546 (67%) of patients at 1 year. The mean baseline DAS-28 decreased over the study years, although remained very high, in keeping with UK guidelines [mean DAS-28 6.38 (0.98) in 2008] (Table 3). The baseline

Table 1 Baseline characteristics of anti-TNF-treated patients by year of first treatment start

Characteristic	2001	2002	2003	2004	2005	2006	2007	2008	*P* for trend
n	119	1206	2930	3138	1553	1056	782	432	
Age, years	53.2 (13.3)	53.9 (11.9)	56.3 (12.1)	56.7 (12.1)	56.5 (12.1)	56.9 (12.9)	56.2 (12.2)	57.0 (12.9)	<0.001
Female, *n* (%)	92 (77)	915 (76)	2242 (77)	2376 (76)	1162 (75)	803 (76)	594 (76)	351 (81)	0.454
Disease duration, years	15.0 (9.2)	13.8 (8.8)	13.9 (9.5)	13.3 (9.7)	12.8 (9.8)	12.5 (10.3)	12.3 (10.3)	11.4 (9.0)	<0.001
Disease duration <5 years, *n* (%)	11 (9)	158 (13)	424 (14)	591 (19)	350 (23)	251 (24)	207 (26)	125 (29)	<0.001
Disease duration <2 years, *n* (%)	0	10 (0.8)	41 (1)	122 (4)	65 (4)	59 (6)	48 (6)	20 (5)	<0.001
Previous number of DMARDs[a]	5.0 (1.7)	4.3 (1.7)	4.2 (1.7)	3.9 (1.6)	3.6 (1.5)	3.6 (1.4)	3.5 (1.4)	3.2 (1.2)	<0.001
Failed only two earlier DMARDs[a], *n* (%)	7 (6)	166 (14)	481 (16)	698 (22)	415 (27)	219 (21)	183 (23)	131 (30)	<0.001
On oral corticosteroids at baseline, *n* (%)	54 (45)	648 (54)	1411 (48)	1422 (45)	628 (40)	387 (37)	244 (31)	133 (31)	<0.001
No baseline comorbidity[b], *n* (%)	46 (41)	490 (42)	1111 (39)	1186 (39)	610 (41)	428 (42)	336 (44)	151 (36)	0.491
>1 baseline comorbidity[b], *n* (%)	26 (22)	262 (22)	762 (26)	779 (25)	382 (24)	264 (25)	160 (20)	111 (26)	0.683

All values are represented as mean (S.D.) unless otherwise specified. [a]Does not include previous corticosteroids. [b]Comorbidity includes one or more of hypertension, ischaemic heart disease, cerebrovascular accident, epilepsy, asthma, chronic obstructive pulmonary disease, peptic ulcer disease, liver disease, renal disease, history of tuberculosis, demyelinating disease, diabetes, hyperthyroidism, depression or history of cancer.

Table 2 Details of anti-rheumatic drug therapy at start of anti-TNF agent

First prescribed biologic	2001	2002	2003	2004	2005	2006	2007	2008	*P* for trend
Etanercept, *n*	74	109	1442	1901	410	3	1	0	
Percentage taken in combination with any DMARD	26 (35)	48 (44)	631 (44)	1044 (55)	262 (64)	2 (66)	1 (100)		<0.001
Percentage taken in combination with MTX	17 (21)	23 (21)	395 (27)	723 (38)	182 (44)	0	0	0	<0.001
Percentage taken in combination with >1 DMARD	11 (15)	11 (10)	160 (11)	282 (15)	87 (21)	0	0	0	<0.001
Infliximab, *n*	45	1068	1067	494	335	250	57	0	
Percentage taken in combination with any DMARD	42 (93)	985 (92)	994 (93)	448 (91)	321 (96)	231 (92)	54 (95)	0	0.382
Percentage taken in combination with MTX	39 (87)	906 (85)	903 (85)	420 (85)	298 (89)	202 (81)	49 (86)	0	0.944
Percentage taken in combination with >1 DMARD	12 (27)	189 (18)	233 (22)	110 (22)	106 (32)	70 (28)	18 (32)	0	<0.001
Adalimumab, *n*	0	29	421	743	808	803	724	432	
Percentage taken in combination with any DMARD	0	12 (41)	237 (56)	503 (68)	611 (75)	614 (76)	573 (79)	328 (76)	<0.001
Percentage taken in combination with MTX	0	7 (24)	156 (37)	376 (51)	452 (56)	451 (56)	428 (59)	269 (62)	<0.001
Percentage taken in combination with >1 DMARD	0	2 (7)	56 (13)	154 (21)	225 (28)	233 (29)	249 (34)	136 (32)	<0.001

Table 3 Baseline disease activity and disability and drug survival by year of anti-TNF start

Outcome	2001	2002	2003	2004	2005	2006	2007	2008	*P* for trend
n	119	1206	2930	3138	1553	1056	782	432[a]	
Baseline DAS-28	6.77 (1.07)	6.75 (0.98)	6.67 (0.98)	6.56 (1.00)	6.51 (0.94)	6.41 (1.00)	6.34 (1.02)	6.38 (0.98)	<0.001
Change in DAS-28 at 6 months	−2.08 (1.52)	−2.20 (1.57)	−2.17 (1.52)	−2.33 (1.50)	−2.33 (1.55)	−2.29 (1.60)	−2.26 (1.53)	−2.31 (1.53)	0.106
Percentage of no response	26.9	22.6	22.5	18.4	19.7	20.6	19.2	20.4	0.008*
Percentage of moderate response	54.8	55.8	56.6	56.7	53.7	49.8	51.3	48.6	
Percentage of good response	18.3	21.6	20.9	24.9	26.6	29.6	29.6	31.0	<0.001**
Percentage of remission	8.1	10.7	10.6	14.1	16.2	16.9	17.9	19.4	<0.001
Change in DAS-28 at 12 months	−2.03 (1.33)	−2.33 (1.60)	−2.35 (1.63)	−2.41 (1.53)	−2.46 (1.61)	−2.38 (1.69)	−2.46 (1.55)	−2.32 (1.70)	0.544
Percentage of no response	27.8	22.7	21.1	16.9	18.4	20.2	16.9	21.3	0.021*
Percentage of moderate response	54.2	55.5	54.0	56.5	51.0	46.8	46.8	49.0	
Percentage of good response	18.1	21.7	25.0	26.6	30.7	33.1	36.3	29.6	<0.001**
Percentage of remission	7.8	12.1	14.5	15.0	18.8	20.9	23.5	17.4	<0.001
Baseline HAQ, mean (S.D.)	2.21 (0.57)	2.14 (0.54)	2.10 (0.55)	2.04 (0.56)	1.98 (0.57)	1.95 (0.59)	1.87 (0.61)	1.87 (0.65)	<0.001
Change in HAQ after 6 months	−0.26 (0.73)	−0.33 (0.47)	−0.32 (0.50)	−0.32 (0.52)	−0.34 (0.52)	−0.33 (0.55)	−0.33 (0.56)	−0.32 (0.52)	0.279
Change in HAQ after 12 months	−0.31 (0.75)	−0.33 (0.50)	−0.33 (0.52)	−0.33 (0.53)	−0.34 (0.53)	−0.35 (0.54)	−0.34 (0.57)	−0.37 (0.55)	0.134
One-year drug survival (proportion; 95% CI)	0.73 (0.63, 0.80)	0.71 (0.68, 0.74)	0.71 (0.69, 0.73)	0.74 (0.73, 0.76)	0.73 (0.71, 0.75)	0.70 (0.68, 0.73)	0.73 (0.70, 0.76)	0.72 (0.63, 0.79)	0.013
Two-year drug survival (proportion; 95% CI)	0.62 (0.52, 0.69)	0.50 (0.47, 0.53)	0.58 (0.57, 0.60)	0.63 (0.62, 0.65)	0.61 (0.59, 0.64)	0.58 (0.55, 0.61)	0.66 (0.62, 0.70)	n/a	<0.001

All values are represented as mean (S.D.) unless otherwise indicated. [a]Only 36% of subjects enrolled in 2008 had reached 12 months of follow-up. **P*-value for any responder *vs* non-responder in each consecutive year. ***P*-value for odds of being in higher response.

HAQ score decreased from 2.21 (S.D. 0.57) in 2001 to 1.87 (S.D. 0.65) in 2008. Although there was a trend towards a greater improvement in both HAQ and DAS-28 scores over the study years, particularly at 12 months, this did not reach statistical significance. Despite this there was a significant improvement year on year in the proportion of patients classified as responders (moderate or good), good responders and in DAS-28 remission. There was a minimal trend towards improved drug survival at both 1 and 2 years, with the lowest drug survival observed among those patients initiating treatment in 2002.

Discussion

The results of this large study demonstrate that, even within the restrictions of the UK health-care system, anti-TNF agents are being used earlier in patients with lesser disease activity and disability, and more often in combination with DMARDS. These observations have been associated with significant increases in treatment response, particularly in the rates of EULAR good response and DAS remission.

We also observed that anti-TNF agents are being used increasingly in older patients. This observation may reflect an increasing comfort of anti-TNF use among prescribing clinicians as data on the use in older patients increases [20, 21]. However, the proportion of patients with comorbid conditions has not significantly changed over the course of the study, suggesting there is likely to be a selection bias towards the use of anti-TNF in healthier patients since comorbidity generally is more common in older RA patients.

It is interesting that although the proportion of patients with disease duration <5 years has increased over the study period, the proportion of patients with very early disease (<2 years) remained low (5% in 2008) and the mean disease duration remained high at 11 years, suggesting that there remains a large proportion of patients who are not receiving anti-TNF therapy until late into their disease. National guidelines state that patients can receive an anti-TNF therapy if they have a DAS-28 >5.1 despite a trial of at least two DMARDs, including MTX, for a period of 6 months each [14]. Presumably, those patients who received anti-TNF therapy early in the study were those patients with the longest disease duration who had been 'waiting' for further effective treatment, thus the high observed number of previous failed DMARDs in the earlier years of the study. However, in 2008, only 30% of patients had tried only two DMARDs before receiving anti-TNF. Why disease duration and the number of DMARDs tried before anti-TNF therapy should not have decreased further over the course of the study is not clear. We did not capture the reasons patients had failed previous DMARDs (e.g. primary inefficacy, secondary inefficacy and adverse events), which could effect the length of time a patient spends on each DMARD. It was also not always clear whether some past DMARDs had actually been received in combination, thus increasing this number. However, it is possible that the responses seen in this study could be improved even further through the earlier introduction of anti-TNF, with a greater proportion of patients receiving these therapies after failing only two DMARDs.

Despite the improvements in disease activity, we did not observe a substantial increase in drug survival. A similar pattern has been observed in other cohorts [9, 12]. Increasing alternative treatment options may, in part, be responsible for this finding, with inadequate responders switching to an alternative anti-TNF or other classes of biologics sooner in the treatment course balanced by good responders remaining on treatment longer. A study of the US PharMetrics claims database found that, between 2000 and 2005, patients were increasingly more likely to switch between anti-TNF agents with a shorter duration of treatment before the change over the years of the study [9]. It is also interesting to note the particularly low 2-year drug survival among patients starting anti-TNF therapy in 2002. This is likely explained in part by the temporary worldwide shortage of etanercept [22], with patients subsequently switching anti-TNF agents for reasons of patient choice rather than non-response or adverse events.

One potential limitation of the study was the restriction of recruitment to the BSRBR of 4000 biologic-naïve patients starting each of the three available anti-TNF agents. This sample size was chosen based on the power to detect a doubling in lymphoma risk among anti-TNF users. As recruitment of patients receiving etanercept was completed in 2005, the results of this study cannot be used to comment on the patterns of specific anti-TNF use in the UK. However, up until 2005, when the study was actively recruiting all three anti-TNF therapies, it was estimated that $\sim$7% of all RA patients in the UK were receiving anti-TNF therapies [23] and that the register was capturing $\sim$80% of these patients. There is no reason to believe that the trend towards earlier prescribing of infliximab and adalimumab would not also be true for patients starting etanercept since 2005.

A further limitation may be the external validity of our results to other health-care systems, which may place different restrictions on the use of anti-TNF therapies. In turn, when comparing registry data from different countries, the differences in prescribing guidelines should be considered. The use of anti-TNF therapy in RA patients in the USA is estimated to be much higher. In the Consortim of Rheumatology Researchers of North America database, 40% of patients with established RA (disease >3 years) and 25% of those with early RA (disease <3 years) had received treatment with anti-TNF [11]. The baseline level of disease also differs from other countries [in 2005, 38% of patients registered in DANBIO (Denmark) had moderate disease activity (baseline DAS-28 between 3.2 and 5.1)]. Whether responses to anti-TNF are higher in these countries is less clear, although good EULAR response rates were estimated to be as high as 50% in Denmark in 2005 [12]. However, even within our very severe patients, we have seen a significant trend towards better outcomes over the past 8 years.

In conclusion, this study has shown that in the UK, anti-TNF agents are being used earlier in disease and increasingly in combination with DMARDs. These changes have been associated with marked improvements in treatment outcome.

Rheumatology key messages

- Patients with RA are receiving anti-TNF therapies earlier in disease.
- Many patients still receive their first anti-TNF drug after the first 5 years of disease.
- Response scores and remission rates have improved significantly since the earliest use of anti-TNF therapy.

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