

Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug

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Objectives. Small studies have shown an improvement in disease activity in patients with RA who have switched between anti-TNF therapies for reasons of inefficacy. However, it is not clear whether switching improves longer term outcomes, such as disability. This analysis compares changes in HAQ scores 1 yr following lack of response to a first anti-TNF based on subsequent treatment during that year.

Methods. Analysis was limited to RA patients with inefficacy to a first anti-TNF based on (i) clinician opinion and/or (ii) disease activity score in 28 joints and had an HAQ measured at time of non-response and 12 months later. Patients were classified into three groups based on treatment during the next 12 months: (i) continued anti-TNF despite non-response; (ii) stopped anti-TNF with no further biologics; and (iii) switched to a second anti-TNF. Mean improvement in HAQ was compared among the groups using multivariable linear regression models.

Results. As of July 2006, 868 patients met the inclusion for this analysis. Four hundred and seventy-nine patients stopped anti-TNF of whom 331 switched to a second anti-TNF. Three hundred and eighty-nine continued treatment. Patients who continued and those who switched had improvements in HAQ over the 12 months, unlike patients who discontinued all biologic therapy. The best improvement was seen in those who switched [adjusted mean improvement in HAQ 0.15 (95% CI 0.26, 0.05)].

Conclusion. There is a significant improvement in HAQ in patients who switch to a second anti-TNF, providing an effective next choice of therapy for some patients who fail to respond to their first anti-TNF.

KEY WORDS: Rheumatoid arthritis, Anti-tumour necrosis factor therapy, Disease-modifying anti-rheumatic drugs, Disability, Treatment response, Switching.

Introduction

Anti-TNF therapies represent a significant advance in the management of severe RA. Randomized controlled trials estimated upwards of 50–70% of patients achieve at least an ACR20 response [1–4]. More recently, observational data of large patient registries have shown similar results with ~70% of patients achieving at least a European League Against Rheumatism (EULAR) moderate response [5]. However, what is inevitable in these data is that approximately one-third of the patients do not achieve these minimum responses. Recent observational data has also shown that ~30% of patients will discontinue their first course of anti-TNF therapy within the first year [6–9].

After failing anti-TNF therapy, the further management options for these patients remain limited. Many will have already failed multiple traditional DMARDs prior to starting their first anti-TNF therapy. Options include yet another trial of traditional DMARDs, or even corticosteroids, continuing on their initial anti-TNF therapy despite an inadequate response or switching to a different biologic agent. Until recently, the choice of switching to a second biologic agent has been limited to switching between anti-TNF therapies and the availability of newer biologic agents remains limited in many countries.

The evidence for switching between anti-TNF therapies in patients who have had lack of response to their first anti-TNF therapy is growing. Many small case series and open-label studies have demonstrated good responses in patients switching for both primary and secondary inefficacy, as well as adverse events [10]. However, the majority of these studies were very small and often combined patients who have switched for inefficacy or adverse

events. The response to a second anti-TNF will differ based on the reason for the switch [11, 12]. In addition, most studies to date have not included a comparison with other treatment options and have only focused on disease activity and not longer term outcomes, such as disability. Therefore, the aim of this analysis was to assess disability in a group of RA patients 12 months after failing to respond to a first anti-TNF therapy, depending on subsequent management over those 12 months.

Patients and methods

Patient selection

Patients for this study were selected from the large British Society for Rheumatology Biologics Register (BSRBR). The details of this study have been described elsewhere [13]. Briefly, as part of the UK national guidelines, patients with RA starting anti-TNF therapy are registered with the BSRBR, the purpose being to systematically follow these patients for short- and long-term outcomes including drug safety and efficacy. The register is still actively recruiting and following new patients starting anti-TNF therapy.

The UK national guidelines recommend that anti-TNF therapies are administered to patients with active RA, defined as a disease activity score in 28 joints (DAS28) >5.1 despite previous therapy with at least two DMARDs, one of which should be MTX. During the period of recruitment, etanercept was administered as a subcutaneous injection either once (50 mg) or twice (25 mg) weekly and adalimumab was administered as a subcutaneous injection 40 mg fortnightly. The suggested starting dose of infliximab was 3 mg/kg administered in conjunction with MTX.

Baseline assessment

Baseline data, including demographics, diagnosis, disease duration, DAS28 [14], past and current anti-rheumatic therapies and comorbidities are collected by the patient's rheumatologist and/or

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rheumatology nurse. In addition, each patient completes a separate questionnaire as well as the HAQ adapted for British use [15].

Follow-up

Rheumatologists are sent a follow-up questionnaire every 6 months. Of relevance to this analysis, the rheumatologist records whether their patient's registered anti-TNF drug has been continued, switched to another biologic drug or stopped. The reasons for stopping or switching treatment are based on the physician's opinion, as recorded in the medical charts, and classified into lack of efficacy, adverse events or other reasons. Changes in non-biologic DMARDs are also captured. In addition, the most recent DAS28 is recorded at each 6-month follow-up. This measurement may or may not correlate with changes in therapy. Patients are contacted separately by post and asked to complete a HAQ score on a 6-monthly basis.

Statistical analysis

This analysis was limited to patients with a physician's diagnosis of RA who were classified as non-responders to their first anti-TNF agent within the first 12 months of therapy. Patients who discontinued their first anti-TNF therapy for an adverse event were excluded. Patients could be classified as non-responders in two separate ways:

- (i) Drug discontinuation: Patients who discontinued their first anti-TNF therapy in the first 12 months of use with the reason listed as 'inefficacy' were classified as non-responders, regardless of changes in their DAS28 score. The date of discontinuation, defined as the first missed dose, was taken as the date of first non-response.
- (ii) EULAR response: Using the DAS28 measured at baseline, 6 and 12 months, patients could also be classified as non-responders based on the EULAR improvement criteria [16]. Response was first assessed in all patients after 6 months. To account for possible secondary inefficacy, patients who were responders at 6 months but non-responders at 12 months were also included. The date of non-response was taken as the date of the first DAS28 score (i.e. 6- or 12-month follow-up date) which classified the patient as a non-responder.

The primary outcome measure in the study was change in HAQ score in the subsequent 12 months following classification as a non-responder. Patients were only included in the analysis if they had a HAQ score recorded within 90 days of the date on which they were first classified as a non-responder and a subsequent HAQ recorded two follow-ups (or 12 months) later.

Non-responders were divided into three separate groups based on subsequent management over the following 12 months (Fig. 1):

- (i) Group 1—'Stoppers': discontinued anti-TNF therapy within the first 12 months and did not start a subsequent anti-TNF agent or other biologic drug during the next 12 months.
- (ii) Group 2—'Stayers': continued on their original anti-TNF agent despite being classified as a non-responder and remained on therapy until at least within 90 days of the final HAQ measurement (i.e. for a minimum of further 9 months).
- (iii) Group 3—'Switchers': stopped their first anti-TNF therapy within the first 12 months of therapy for non-response but started a second anti-TNF therapy during the subsequent 12 months. To capture the full experience of patients who switched between anti-TNF therapies, Group 3 included all patients who started a second anti-TNF at any time during the next 12 months. As this group was quite varied, we also identified a group of patients within Group 3 who switched early (within 90 days of being classified as a non-responder)

and remained on the second anti-TNF therapy at least until within 90 days of the second HAQ measurement (Group 4—'Early Switchers') to ensure at least 6 months treatment with the second anti-TNF therapy.

Baseline characteristics (at the start of the first anti-TNF therapy) were compared among the groups using Pearson chi-squared and Kruskal–Wallis tests. The primary outcome was the mean change in HAQ score in the 12 months following classification as a non-responder. This outcome was compared between those patients who discontinued all biologic therapy (Stoppers) and each of the other three treatment groups, using multivariable linear regression models. The models were adjusted for age, gender, disease duration, DAS28 score at the start of first therapy, DAS28 score at first non-response and HAQ score at first non-response, as it was felt that these factors may have influenced which treatment group patients were allocated to and may also have influenced any further change in HAQ during the follow-up period. All analysis was performed in STATA Version 9.2 [College Station (TX), Stata Corporation] [17].

Ethical approval

The BSRBR received ethical approval from the United Kingdom North West Multi-centre Research Ethics Committee (MREC 00-8-53). Written informed consent was obtained from the participants according to the Declaration of Helsinki [18].

Results

As of July 2006, a total of 10 993 patients with RA were registered with the BSRBR. Of these, 4458 (41%) started etanercept, 3956 (36%) infliximab and 2579 (23%) adalimumab as their first anti-TNF drug. As of July 2006, 9026 (82%) had reached at least 6 months of follow-up, 7640 (69%) at least 1 yr, 5885 (53%) at least 18 months and 5002 (46%) at least 2 yrs of follow-up. During the first 12 months, 424 had stopped their first anti-TNF drug for an adverse event and were not included in this analysis. During this same period, 978 patients had stopped for inefficacy (726 with an HAQ recorded within 90 days of stop date) and 1925 were classified as EULAR non-responders based on change in DAS28 (1384 with a HAQ recorded within 90 days of DAS28 date). As many patients who stopped for inefficacy were also classified as non-responders using the EULAR response, a total of 1725 patients were classified as non-responders and had a HAQ score recorded within 90 days of being classified as a non-responder (Fig. 1). The majority of these non-responders (88%) were classified as non-responders at 6 months and 12% were classified at 12 months.

Of the 1725 non-responders, 1222 (71%) had completed a further 12 months of follow-up. Of these, 1033 (85%) patients had a HAQ score recorded at this later follow-up. Of these 1033 non-responders, 148 (14%) received no further anti-TNF therapy during the subsequent 12 months (Stoppers), 331 (32%) switched to a second anti-TNF therapy (Switchers) and 389 (38%) continued on their first anti-TNF therapy for at least a further 9 months (Stayers), giving a total of 868 patients for this analysis (Table 1). The remaining patients continued on their first anti-TNF therapy beyond the date of non-response but discontinued within the next 9 months and were not included in this analysis, as disability measures did not correlate with drug discontinuation.

Compared with patients who were either Stayers or Switchers, Stoppers were slightly older (61 vs 58 yrs, $P=0.01$) when starting their first anti-TNF therapy (Table 2). Stayers tended towards a lower HAQ and DAS28 at the start of their first anti-TNF therapy (Tables 2 and 3). Overall, the mean change in HAQ score with the first anti-TNF agent in this group of non-responders (measured at the point of first designation as non-responder) was -0.08 U (s.d. 0.32), demonstrating a small improvement. However, when comparing the improvements between the three groups, Stayers

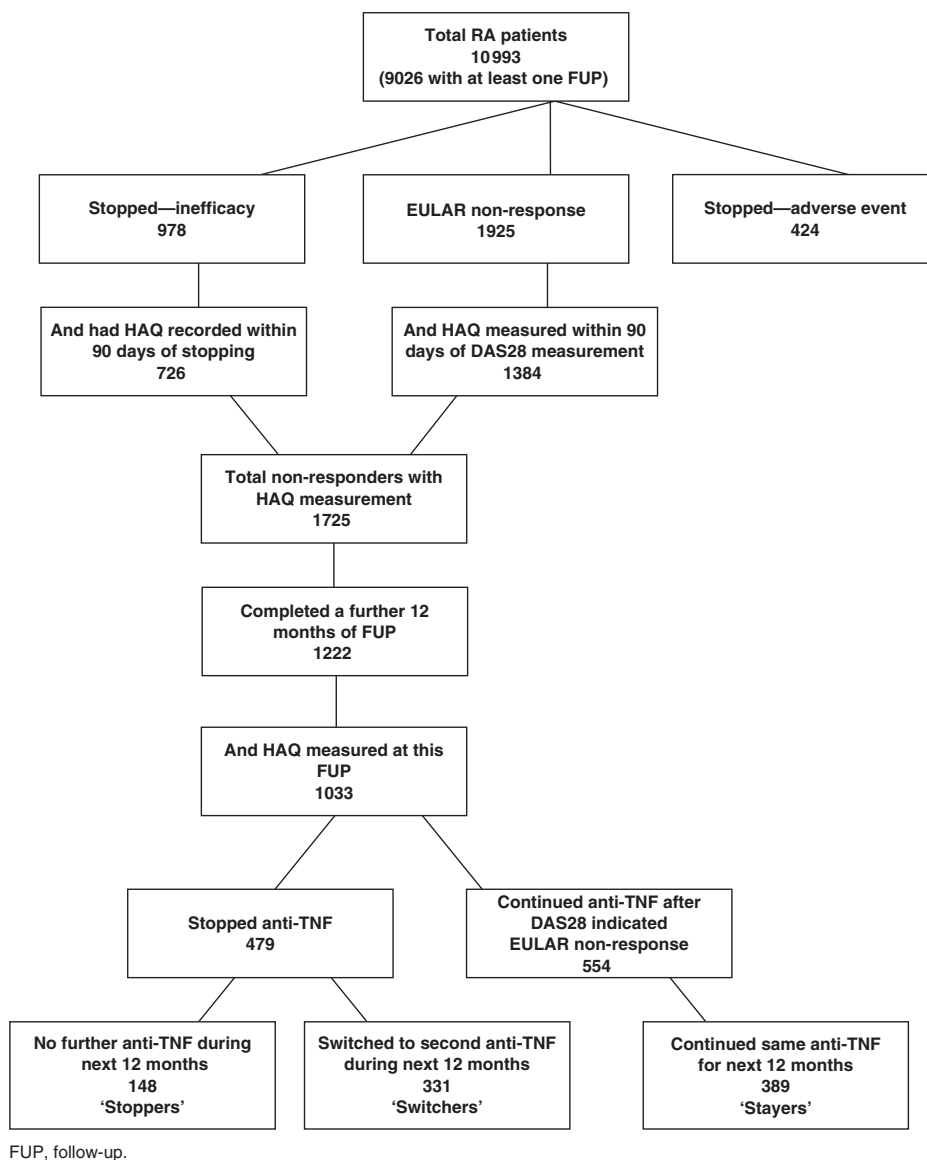


FIG. 1. Patient flow. FUP, follow-up.

had a greater mean improvement in HAQ score with the first anti-TNF therapy compared with both Stoppers and Switchers (Table 3).

During the subsequent 12 months, Stoppers experienced no change in their mean HAQ score. The greatest mean improvement in HAQ score in the 12 months after classification as non-responders was observed among Switchers, with Stayers falling in between. This trend remained after adjusting for differences in age, gender, disease duration, HAQ score and DAS score (at start of first anti-TNF therapy and at time of failure).

As these scores represent mean improvements among the groups, the proportion of patients who achieved a minimum clinically important difference (MCID) (defined as improvement in HAQ score of at least 0.22 U) [19] were also identified. Among Stoppers, only 22% reached this MCID compared with 31% of Stayers and 36% of Switchers ($P < 0.01$ compared with Stoppers). The best response (46%) was seen among patients who switched anti-TNF therapy early ($n = 147$) following inefficacy and remained on therapy for at least 6 months (Early Switchers), which was significantly greater than Stayers (31%) ($P < 0.01$).

To explore the possible effects of background DMARD therapy, the proportion of patients receiving DMARDs with their first anti-TNF drug and the proportion that had a change

to therapy during the subsequent 12 months were analysed. Overall, 61% of patients were receiving a DMARD with their first anti-TNF therapy, which did not differ significantly among the groups (Table 2). The majority of these patients were receiving MTX (49% of all patients, 80% of all DMARD prescriptions). Only 13% of Stayers reported a change in DMARD therapy over the subsequent 12 months (change in dose or new DMARD) compared with 32% of Stoppers and 32% of Switchers ($P < 0.05$).

Discussion

Data from small open-label studies and clinical trials have shown that patients who are not responding to a first anti-TNF drug can gain significant improvements in disease activity when switched to a second anti-TNF agent [10] and a recent clinical trial has suggested that this improvement will exceed any further improvement in disease activity which may be expected from staying on the less effective drug [20]. Our data suggest that patients who do not respond to a first anti-TNF drug may also subsequently gain improvements in HAQ score, if switched to a second agent.

Why patients should respond to one anti-TNF and not another, despite similar mechanisms of action, remains unexplained, but possible hypotheses include differential bioavailability of these drugs, differences in stability of the drug-TNF complex and the development of anti-drug antibodies [21]. Differences in patient adherence among these three agents may also play a role. Unfortunately, the relatively small number of patients who switched therapy in this analysis precluded any specific between-drug comparisons.

Inherent to this analysis is the limitation of using observational data to measure treatment response. Thus, while the analysis did capture outcomes among patients as they occurred in the real world, there is no doubt that there was still some selection of patients as to whether they started any anti-TNF therapy in the first instance, whether they stopped therapy if they were not responding adequately, and later whether they switched to a second agent. Decisions on treatment and thresholds for stopping will have changed over the course of this study, due to availability of different anti-TNF agents and physicians' experience over time, which may act to limit the external validity of these results. We attempted to adjust for factors which may have influenced a physician's decision to start and stop therapy, including age, disease duration, DAS28 and HAQ scores, and found that this actually made little difference to the results. Further adjustment used to model physicians' decisions using inverse probability of treatment weighting [22], which included DAS28 scores 6 months after a patient was classified as a non-responder, were also employed, but did not alter the results (data not shown). Unfortunately, as discussed subsequently, missing DAS28 scores excluded many patients from this model. There is also a strong possibility that other unmeasured confounders, particularly

related to the patient, may have influenced these results. Although all of these patients were classified as non-responders, only half stopped therapy and only two-thirds of these switched to a second agent. Factors such as past experience of DMARD therapy, the occurrence of minor adverse events alongside the lack of response and other psychological factors may have influenced a patient's decision to switch to a second anti-TNF agent. These same factors may also have influenced the patients' HAQ scores. In addition, as during the main BSRBR study, HAQ scores were not obtained at the time of treatment decisions but rather at regular 6-month intervals, we had to exclude a proportion of patients in order to only use those scores that did correlate with changes to treatment or measures of disease activity. It is possible that the outcomes of these excluded patients may have differed.

In this large cohort of anti-TNF-treated RA patients, over 50% of patients remained on therapy despite a sub-optimal response. Interestingly, this group of patients continued to gain further improvements in HAQ score, despite fewer changes to background DMARD therapy. Why so many patients should remain on a therapy without a significant improvement in DAS28 remains unclear. In the UK, practice guidelines suggest that patients should discontinue therapy if an improvement in DAS28 of at least 1.2 U is not achieved after 3 months (or after 6 months if other improvements in disease had been observed at 3 months) [23]. The treatment options in the UK at the time of this analysis (as of July 2006) for patients who had failed anti-TNF therapy were limited to stopping anti-TNF therapy and reverting to traditional DMARDs and/or corticosteroids, continuing anti-TNF therapy despite a lack of response or switching to a second anti-TNF agent. Both rituximab and abatacept received a European licence in 2007, a year following this analysis. Initial UK guidelines [23] for the use of anti-TNF agents in RA did not recommend switching between therapies, and therefore many hospitals may have been unable to obtain funding for a second course of anti-TNF therapy. As most of these patients had already failed on average four DMARDs, there likely remained no other alternative other than continue a less effective therapy. However, we also observed that the best improvement in HAQ scores with the first anti-TNF therapy were observed among patients who subsequently remained on therapy, and therefore, it is possible that despite a lack of significant improvement in DAS28, patients may have felt better and therefore, their rheumatologist elected to maintain this therapy despite a suboptimal response. It is also likely that, due to reasons discussed earlier, patients may also have been kept on their second anti-TNF drug despite a lack of response, and therefore our measurement of response among Switchers may also be an underestimate of the treatment effect.

The primary outcome measure chosen in this analysis was mean change in HAQ score in the 12 months following non-response to a first anti-TNF therapy. The HAQ was selected as it is a good measure of longer-term outcomes in arthritis. However, in patients with long-standing RA, HAQ scores may correlate more with damage rather than with disease activity, and it has been shown that HAQ scores are less responsive to treatment at this later stage [24]. The median disease duration in this cohort was 12 yrs. However, despite this possible limitation, HAQ scores

TABLE 1. Details of anti-TNF therapy

	First anti-TNF (n = 868)	Second anti-TNF (n = 331)
Etanercept (%)	44	45
Infliximab (%)	37	17
Adalimumab (%)	19	38

TABLE 2. Characteristics of patients at start of first anti-TNF therapy

	Stoppers (148)	Stayers (389)	Switchers (331)	Early Switchers (147)
Age (yrs)*	61 (53, 68)	58 (49, 66)	58 (49, 65)	57 (49, 64)
Female, n (%)	120 (81)	314 (81)	263 (79)	116 (79)
Disease duration (yrs)	12 (7, 19)	12 (6, 19)	11 (6, 19)	12 (6, 20)
DAS28*	6.6 (5.9, 7.3)	6.3 (5.6, 6.9)	6.7 (6.1, 7.5)	6.6 (6.0, 7.4)
Previous DMARDs	4 (3, 6)	4 (3, 5)	4 (3, 6)	4 (3, 6)
DMARD, n (%)	82 (55)	241 (62)	210 (63)	91 (62)
MTX, n (%)	73 (49)	200 (51)	156 (47)	70 (48)
Oral steroid [†] , n (%)	89 (58)	187 (48)	157 (47)	63 (42)
NSAID, n (%)	84 (57)	247 (64)	220 (66)	105 (71)

*Difference observed between Stoppers, Stayers and Switchers, $P < 0.01$. [†]Difference observed between Stoppers, Stayers and Switchers, $P = 0.07$. All results are given in median (IQR) unless stated.

TABLE 3. Mean changes in HAQ scores

Group	HAQ at start of first anti-TNF therapy mean (s.d.)	HAQ when classified as non-responder mean (s.d.)	Mean change in HAQ score on first anti-TNF therapy ^a , Mean (s.d.)	HAQ measured 12 months after non- response mean (s.d.)	Adjusted ^b change in HAQ over 12 months Mean (95% CI)	Patients with at least 0.22 U improvement in HAQ over subsequent 12 months ^c n (%)
Stoppers (148)	2.21 (0.48)	2.19 (0.51)	-0.03 (0.37)	2.19 (0.56)	Referent	33 (22)
Stayers (389)	2.08 (0.54)	1.96 (0.60)	-0.13 (0.20)	1.90 (0.59)	-0.12 (-0.23, -0.02)	123 (31)
All Switchers (331)	2.15 (0.48)	2.10 (0.52)	-0.05 (0.31)	1.98 (0.60)	-0.15 (-0.26, -0.05)	120 (36)
Early Switchers (147)	2.10 (0.52)	2.03 (0.58)	-0.07 (0.41)	1.90 (0.66)	-0.18 (-0.31, -0.06)	61 (42)

^aUsing HAQ scores measured at start of first anti-TNF therapy and at time of first designation as non-responder. ^bAdjusted for age, gender, disease duration, HAQ at first failure, DAS28 at start of first anti-TNF, DAS28 at first failure. ^cDifference in proportion between Stayers/Stoppers and Switchers/Stoppers ($P = 0.01$). Difference between All Switchers and Stayers ($P = 0.19$). Difference between Early Switchers and Stayers ($P = 0.03$).

can still improve significantly in patients with long-standing disease following effective disease control. During clinical trials of anti-TNF therapies in biologically naive patients, the mean improvement in HAQ score in the active treatment arms was in the range of 0.5 U over 6–12 months [1–3]. However, it may not be realistic to expect such an improvement among a group of patients who have already failed one anti-TNF agent. Patients are also more likely to stop a second anti-TNF agent for inefficacy if they had also stopped their first agent for inefficacy [25]. Thus, while the degree of response among individual patients who do respond to a second anti-TNF drug may be equivalent to that seen with a first agent, the proportion of patients who do respond will be lower and thus, the mean improvement among a group of patients will also be lower.

DAS28 was not selected as the primary outcome measure for two main reasons. First, it was felt that, in this uncontrolled study, where other non-biologic therapies are allowed, changes in DAS28 over 12 months may not necessarily reflect only changes to anti-TNF therapies. Short-term interventions, such as corticosteroid injections, are as likely to reduce swollen and tender joint counts and ESR. Whilst we have shown that DMARD use did not vary significantly between the groups in the subsequent 12 months' of follow-up, unfortunately, we did not record details of joint injections or details of intra-muscular injections, which may also have had an influence upon DAS28 scores. In addition, we found that over time, patients were less likely to have a DAS28 recorded, particularly if anti-TNF therapy was discontinued or if there had been no changes to therapy for a prolonged period of time.

In conclusion, patients with long-standing disease who do not respond to their first anti-TNF therapy discontinue this first drug and receive no biologic therapy in the subsequent 12 months do not experience any further mean improvements in HAQ score over this 12-month period. Patients who continue on their first anti-TNF drug despite a suboptimal improvement in DAS28 gain some further improvement in HAQ score, suggesting that biologics may continue to provide additional benefit to patients beyond the first few months of treatment. However, the best response was seen among patients who switched to a second anti-TNF therapy.

Rheumatology key messages

- Many patients who fail to respond to one anti-TNF agent switch to a second anti-TNF drug.
- A significant proportion of these patients will demonstrate improvements in HAQ score on their second drug.

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