Concise Report

Discrepancies between the EULAR response criteria and the NICE guidelines for continuation of anti-TNF therapy in RA: a cause for concern?

S. Jerram, S. Butt, K. Gadsby and C. Deighton

Objectives. A discrepancy exists between the National Institute for Health and Clinical Excellence (NICE) guidelines for continuation of TNF therapy in RA and EULAR response criteria. We performed a retrospective study of patients starting anti-TNF therapy to establish how many NICE non-responders would have met EULAR response criteria, and whether this may increase.

Method. We calculated the percentage of NICE non-responders who would have met EULAR moderate response criteria. We then compared the mean decrease in disease activity score (DAS28) for patients with low and high baseline scores. We analysed trends for treating RA in Derby with anti-TNF to address whether we were treating less active disease over time.

Results. At 3 months \( (n=271) \) patients, 7.7% of NICE non-responders would have met EULAR moderate response criteria. At 6 months \( (n=240) \) this was 23.7%. Patients starting with a higher DAS28 had a significantly greater absolute drop in score. The mean decrease between the 1st and 3rd tertiles of patients divided by baseline DAS28 was significant at 3 and 6 months \( (P<0.001) \). Derby rheumatologists were treating less active RA over time. Comparing the mean DAS28 baseline between the 1st and 3rd tertiles of patients divided by anti-TNF commencement date was significant \( (P<0.001) \).

Conclusions. A significant minority of NICE non-responders would fall within the moderate EULAR response criteria. This is likely to increase in future due to the increasing tendency to initiate anti-TNF in patients with less active disease. Consequently, NICE guidelines should be brought in line with EULAR response criteria.

KEY WORDS: Rheumatoid arthritis, Biological therapies,Outcome measures, Health policies.

Introduction

The disease activity score (DAS) was developed in order to provide a quantifiable measure of RA disease activity [1, 2]. It is derived from a combination of information on swollen joints, tender joints, the acute phase response and general health. Since it was originally created in 1993, the DAS has been found to have a greater power than other indices or single variables to discriminate low from high disease activity [3]. Good correlation over time between DAS and increased joint damage has also been found [4].

The DAS28 is a modified version of the original DAS, based on the same four variables, but with a reduced joint count of 28 for swollen and tender joints. Despite the reduction in joints counted, the DAS28 has a high correlation with the original DAS, and has been validated to a similar degree [5]. The EULAR response criteria were devised as a means of measuring efficacy of treatment using DAS and DAS28 [6]. They incorporate both an absolute measure of disease activity, and a measure of change in activity. Patients are considered to have shown a good response if their DAS28 is \( \leq 3.2 \) and has decreased by \( >1.2 \). A moderate response is defined as a DAS28 \( \leq 3.2 \) plus a decrease \( >0.6 \) and \( \leq 1.2 \), or a DAS28 \( \leq 5.1 \), or a DAS28 \( >3.2 \) and a decrease \( >0.6 \), or a DAS28 \( >5.1 \) and a decrease \( >1.2 \) (Table 1). Subsequent studies have validated the response criteria. Patients who showed a good or moderate EULAR response to treatment demonstrated a significantly greater improvement in functional capacity, and less progression of joint damage than patients with no EULAR response [6, 7].

The 2001 British Society for Rheumatology guidelines on anti-TNF therapy in RA [8] (updated in 2005 [9]) recommended that therapy should not be continued where there is a lack of response after 3 months, defined as an improvement in DAS28 \( >1.2 \). These guidelines were included unchanged in the National Institute for Health and Clinical Excellence (NICE) Technology Appraisal in 2003 [10], and again in the NICE Final Appraisal Determination of November 2006 [11]. The EULAR response criteria for treatment of RA (Table 1) include in the category of ‘moderate responders’ patients who show a drop in DAS28 \( \leq 1.2 \) and \( >0.6 \), provided their DAS28 is \( \leq 5.1 \) at assessment (middle box of Table 1). Thus there is a discrepancy between the NICE guidelines and the EULAR response criteria. Patients who fall into the ‘middle box’ would not be eligible for continuation of anti-TNF therapy under the BSR and NICE guidelines, despite demonstrating an EULAR moderate response to treatment. Furthermore, the latest NICE guidelines require patients to have ongoing 6-monthly assessments, where if their DAS28 goes within 1.2 of their baseline DAS they will no longer be eligible to continue on treatment [11]. Because NICE now require demonstration of ongoing response, discrepancies between EULAR and NICE response criteria are all the more important for close scrutiny.

When anti-TNF was first introduced into clinical practice, it was primarily used in patients with high baseline DAS28 who had failed on many DMARDs and had long disease duration. For example, the initial report of the British Society for Rheumatology Biologics Register reported that patients had a mean baseline DAS of 6.6 (despite 49% being on steroids), failure on a median of 4 DMARDs, and a mean disease duration of 14 yrs [12]. Such patients would have been unlikely to fall into the ‘middle box’ EULAR moderate response category, because in order to achieve a DAS28 \( \leq 5.1 \) after treatment they would almost certainly have shown a drop in DAS28 of \( >1.2 \) from baseline. However, as anti-TNF therapy in RA is rolled out across a wider disease population, it is probable that it is being provided to increasing numbers of patients with lower baseline DAS28s. Patients who have a lower baseline DAS28 may be more likely to see a smaller
absolute DAS decrease after treatment, which would increase the likelihood of them falling into the 'middle box'. Therefore, there may be an increase in the number of patients who have exhibited a moderate EULAR response, but are denied continuation of treatment under the current NICE guidelines.

We performed a retrospective audit of patients screened for anti-TNF therapy in the Rheumatology Department of Derbyshire Royal Infirmary, in order to establish:

(i) The number of patients who fulfil EULAR moderate response criteria but not the NICE guidelines for continuation of therapy at 3- and 6-month assessments;
(ii) Whether there is a significant difference in DAS decrease between patients with high and low initial baseline DAS28;
(iii) Whether the profile of patients going on to anti-TNF therapy in Derby is shifting to include patients with lower baseline DAS28.

Method

In order to establish whether any patients fulfilled EULAR moderate response criteria whilst failing to fulfil NICE response criteria, baseline DAS28 and DAS28 decreases at 3 and 6 months were collected. The data were analysed to establish the number of patients at both 3 and 6 months who had a DAS28≤5.1 and a DAS drop ≤1.2 and >0.6.

In order to establish whether patients with lower baseline DAS28s were more likely to have a lower drop in DAS28, patients were divided into tertiles on the basis of their baseline DAS28s, and mean DAS decrease after 3 and 6 months was calculated for each of the three groups. The mean DAS decreases between the three tertile groups were compared using independent t-tests.

In order to establish whether there had been a tendency over time in Derby to treat patients with lower baseline DAS28s, patients were divided into tertiles on the basis of date of commencement on anti-TNF therapy, and the mean baseline DAS28 was calculated for each of the three groups. The mean baseline DAS28s were compared using independent t-tests. It was of interest to also see if there had been a tendency to treat disease earlier over time. The mean disease durations for each of the temporal tertiles were also compared using independent t-tests. The study was registered with the Audit Committee of the Derbyshire Royal Infirmary.

Results

Baseline DAS28 and 3-month DAS28 were available for 271 patients. According to NICE criteria, 245 (90.4%) were responders. Of the 26 non-responders, 2 (7.7% of NICE non-responders, 0.73% or all patients) had a 3-month DAS28 of <5.1 and a DAS decrease >0.6 but ≤1.2, and would thus fall into the ‘middle box’ of the EULAR moderate response criteria (Table 1). Baseline DAS28 and 6-month DAS28 were available for 240 patients. According to NICE criteria, 202 (84.2%) were responders. Of the 38 non-responders, 9 (23.7% of NICE non-responders, 3.75% or all patients) would fall into the ‘middle box’ of the EULAR response criteria (Table 1). Of the nine cases who fall into the middle box of moderate EULAR response criteria at 6 months, seven had DAS28 at baseline that fell into the lowest 10% of the distribution.

The 271 patients with data available at 3 months were divided into equally distributed tertiles by baseline DAS28, and mean DAS difference was calculated for each tertile. The differences in mean between the three tertiles were all significant, and showed a trend of decreasing DAS28 changes in patients with decreasing baseline DAS28 (Table 2). The 240 patients with data available at 6 months were similarly divided into tertiles by baseline DAS28, and mean DAS difference calculated for each tertile. The difference in mean between tertiles 1 and 3 and tertiles 2 and 3 were significant. The difference in mean between the 1st and 2nd tertiles narrowly failed to reach significance. Again, the figures showed a trend of decreasing DAS28 changes in patients with decreasing DAS28 (Table 1). Patients in the lowest 10% of baseline DAS28 showed a mean DAS decrease at 6 months of 1.3615. This is close to the DAS decrease of 1.2 which marks the cut-off point for continuation of anti-TNF treatment under the NICE guidelines.

In total, 300 patients on the database have been commenced on anti-TNFs. Tertiles of this population by date of commencement on anti-TNFs fell into the ranges: 3 April 2001 to 6 July 2004, 7 July 2004 to 11 April 2006 and 12 April 2006 to 11 July 2007. Mean baseline DAS28s for the three tertiles were 7.41, 7.11 and 6.77, respectively, with a trend of reduction in mean DAS28 for more recent cases. The mean differences in tertiles were all significant (1st vs 2nd 95% CI 0.0678–0.529, t = 2.552, P = 0.011; 2nd vs 3rd 95% CI 0.110–0.571, t = 2.908, P = 0.004; 1st vs 3rd 95% CI 0.415–0.862, t = 5.638, P < 0.001). Mean disease duration values for each of the three tertiles of the population by date of commencement were 17.85, 13.55 and 11.55 yrs. The difference in means was significant between the 1st and 2nd tertiles and the 1st and 3rd tertiles (1st vs 2nd 95% CI 1.18 to 4.61, t = 3.369, P = 0.001; 1st and 3rd 95% CI 3.60–9.03, t = 4.544, P < 0.001). The difference in means between the 2nd and 3rd tertiles was not significant (95% CI 0.61 to 4.61, t = 1.51, P = 0.133).

Discussion

The current NICE guidelines for the continuation of anti-TNF therapy are in effect a simplification of the EULAR response criteria. Whereas the EULAR criteria take into account both DAS decrease and actual DAS28 after treatment, the NICE guidelines only consider DAS decrease. As a consequence, patients who have only experienced a modest DAS decrease of ≤1.2 and >0.6 are not eligible for continuation of treatment under the NICE guidelines, even if they have achieved an actual DAS28 of ≤5.1, which would place them within the category of moderate

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Table 1. The EULAR response criteria

<table>
<thead>
<tr>
<th>Change in DAS28</th>
<th>&gt;1.2</th>
<th>Moderate</th>
<th>&gt;0.6 and ≤1.2</th>
<th>None</th>
<th>≤0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline DAS28</td>
<td>≥5.1</td>
<td>Moderate</td>
<td>&gt;5.1 and &gt;3.2</td>
<td>Good</td>
<td>≤3.2</td>
</tr>
</tbody>
</table>

Table 2. Comparison of the mean DAS28 decreases at 3 and 6 months when the population is divided by baseline DAS28 into equally sized tertiles

<table>
<thead>
<tr>
<th>DAS28 response assessment at 3 months (n = 271 patients)</th>
<th>Baseline DAS28 tertile range</th>
<th>Mean DAS difference between baseline and assessment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st tertile (mildest)</td>
<td>&gt;5.13, ≤5.72</td>
<td>2.0867</td>
</tr>
<tr>
<td>2nd tertile (moderate)</td>
<td>&gt;6.72, ≤7.55</td>
<td>2.523</td>
</tr>
<tr>
<td>3rd tertile (most severe)</td>
<td>&gt;7.55, ≤9.07</td>
<td>3.128</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAS28 response assessment at 6 months (n = 240 patients)</th>
<th>Baseline DAS28 tertile range</th>
<th>Mean DAS difference between baseline and assessment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st tertile (mildest)</td>
<td>&gt;5.13, ≤6.85</td>
<td>2.100</td>
</tr>
<tr>
<td>2nd tertile (moderate)</td>
<td>&gt;6.85, ≤7.61</td>
<td>2.477</td>
</tr>
<tr>
<td>3rd tertile (most severe)</td>
<td>&gt;7.61, ≤9.07</td>
<td>3.011</td>
</tr>
</tbody>
</table>

*Comparison of mean DAS differences at 3 months: 1st vs 2nd tertiles 95% CI −0.778 to 0.0949, t = 2.52, P = 0.013; 2nd vs 3rd 95% CI −0.916 to −0.290, t = 3.80, P = 0.001; 1st vs 3rd 95% CI −1.39 to −0.689, t = 5.84, P < 0.001. Comparison of mean DAS differences at 6 months: 1st vs 2nd tertiles 95% CI −0.780 to 0.0263, t = 1.846, P = 0.067; 2nd vs 3rd 95% CI −0.926 to −0.142, t = 2.693, P = 0.008; 1st vs 3rd 95% CI −1.31 to −0.513, t = 4.516, P < 0.001.
responders under the EULAR response criteria. When anti-TNF was first introduced into RA clinical practice this discrepancy was less of a concern than it is now, because our study shows that in Derby (and we are sure elsewhere) we are using the drug in RA with baseline DAS28s closer to 5.1 as time has gone by, and that patients with lower baseline DAS28 are likely to get less of a drop in their DAS28.

Currently, NICE response criteria are determined at a 3-month assessment, and if the patient satisfies the criteria they are eligible to continue on anti-TNF thereafter [10]. Although the current Final Appraisal Document of the NICE re-appraisal of anti-TNF in RA is going through an appeal process at the time of writing, this will not influence the change to assessing response. This will be conducted at 6 months after commencement and every 6 months thereafter [11]. Our retrospective study shows that although there is not too much of a discrepancy between NICE and EULAR response criteria at the current assessment time of 3 months, this changes substantially at 6 months. Close to a quarter of RA patients who were commenced on anti-TNF therapy in Derby but fell outside the NICE guidelines for continuation of therapy after 6 months met the EULAR criteria for moderate response to treatment. The EULAR criteria are evidence-based [6, 7], whereas the NICE criteria are not. The effect of taking a patient off anti-TNF therapy, despite demonstrating a moderate EULAR response, could be profound. Patients who demonstrate a moderate response would have seen a significant improvement in their symptoms over the course of their 6 months anti-TNF treatment.

There are major concerns about retaining a DAS28 of >5.1 as a barrier that needs to be overcome to be eligible to go onto anti-TNF for RA in the UK [13, 14]. However, if this barrier is to be maintained, we feel that there is a strong case to be made for bringing the NICE guidelines for continuation of anti-TNF therapy into line with the EULAR response criteria. Our data suggest that the discrepancies between the NICE and EULAR response criteria will be intensified by the introduction of 6-month assessments with the new NICE guidelines, and by the increasing tendency to treat less active RA.

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### References


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### Rheumatology key messages

- Just under a quarter of patients assessed at 6 months fulfil EULAR criteria for moderate response to anti-TNF for RA, but do not fulfil NICE response criteria.
- This proportion is likely to increase in the future as the drugs are used in less active disease.
- The NICE response criteria should be brought in line with EULAR criteria if the barrier of a DAS28 >5.1 is to be maintained as a criterion for eligibility.