Concise Report

The importance of the baseline Disease Activity Score 28 in determining responders and non-responders to anti-TNF in UK clinical practice

N. Smith, T. Ding, S. Butt, K. Gadsby and C. Deighton

Objectives. The NICE re-appraisal of anti-TNF requires demonstration of ongoing response, making the baseline 28-joint Disease Activity Score (DAS28) crucially important. A retrospective analysis of all RA patients on their first anti-TNF determined predictive factors for those classified as non-responders at 6 months according to current NICE guidelines.

Methods. The patients were divided into responders (DAS28 dropped by >1.2) and non-responders. These groups were compared for demographics, DAS28 at the two pre-assessments 1 month apart and at baseline. Exposure to intramuscular, oral and IA steroids in the 3 months period before the baseline DAS28 was recorded.

Results. At 6-month assessment in 256 patients, 82.8% were responders with no demographic differences between them and non-responders. Although the first pre-assessment score was not significantly different (6.8 vs 6.6), the second pre-assessment score (7.1 vs 6.7) and the baseline DAS28 (7.2 vs 6.3) were lower in the non-responders (P<0.04 and P<0.001, respectively). Comparing the differences in DAS28 from the first pre-assessment to baseline, the responders had increased by 0.4, and the non-responders had decreased by 0.4, (P<0.001). If the first pre-assessment score had been taken as the baseline DAS28, then 9.4% of responders would be re-classified as non-responders, and 31.8% of non-responders would be re-classified as responders. The proportion of patients who had steroid treatment within the 3 months period before the baseline DAS28 did not differ significantly between the responders and non-responders (34% vs 41%, P=0.38).

Conclusion. Baseline DAS28 is critical in classifying responders at the 6-month assessment.

Key words: Rheumatoid arthritis, Anti-tumour necrosis factor therapies, Outcome measures, Baseline Disease Activity Score 28.

Introduction

RA is a complex inflammatory arthritis where disease activity cannot be assessed using a single physical or laboratory measure. In 1993, the Disease Activity Score (DAS) was developed to provide a quantifiable composite measure of RA disease activity [1,2]. It was derived from a combination of information on swollen and tender joints, the acute-phase response and general health, and applying statistical measures including discriminant and multiple regression analysis. The DAS has been found to show a greater power than other indices or single variables to discriminate low from high disease activity [3] and the area under the curve of CRP correlates well with joint damage over time [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].

In recent years, anti-TNF drugs have revolutionized the treatment of RA. The British Society for Rheumatology (BSR) first issued guidelines in 2001 [6] (updated in 2005 [7]) for the use of anti-TNF agents in the treatment of RA, recommending that patients should have a 28-joint DAS28 of >5.1 U on at least two occasions, 1 month apart, prior to commencing treatment. It also stated 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 based on the European League Against Rheumatism (EULAR) response criteria, but were a non-validated simplification, removing the opportunity for some patients classified as ‘moderate’ responders on the EULAR criteria to be classified as responders according to the BSR criteria [8]. These original 2001 BSR guidelines were included unchanged in the National Institute for Health and Clinical Excellence (NICE) Technology Appraisal in 2002 [9].

In the NICE reappraisal of anti-TNF in RA, the Final Appraisal Determination published in November 2006, includes a significant change in the time frame for response criteria that have to be fulfilled to continue on the drug [10]. Previously, patients had to have a drop of ≥1.2 on a DAS28 at 3-month assessment to continue, but were then deemed responders thereafter without further assessment. This has now changed to 6 months, but needs to be repeated every 6 months thereafter. If at any 6-month assessment a patient’s DAS28 comes within 1.2 of the baseline DAS28, they are deemed to have lost of or no response. The rationale behind this change was to take into account the need to ensure stability of other clinical factors including comorbidities such as concurrent infections and changes in the use of other drugs such as steroids [10]. This makes the baseline DAS28 of critical importance. If a patient has a baseline DAS28 that under-represents their usual disease activity prior to anti-TNF therapy, this might increase the likelihood of subsequent assessments suggesting a loss of, or no response.

Often, in routine clinical practice temporary symptom-relieving interventions, such as steroid injections, are withheld before and during the pre-assessment period, in order to avoid a short-term improvement that may result in failure to meet the eligibility criteria at the pre-assessment. Steroids might also reduce the baseline DAS28, thus penalizing the patient when subsequent 6-month assessments are performed, because it may increase the chances of the patient being classified as a non-responder. If this is the case, health care professionals might be less likely to use...
steroids before and during the pre-assessment period, thus potentially increasing the discomfort of this delay for the patient. This might be a further argument for removing the pre-assessment over the course of a month [11].

We performed a retrospective analysis of all RA patients on their first anti-TNF in the Rheumatology Department of Derbyshire Royal Infirmary, in order to establish:

(i) At 6-month assessments, whether there are significant differences in demographics, disease and baseline DAS28 between the anti-TNF responders (DAS28 dropped by ≥1.2) and non-responders.

(ii) Whether giving any form of steroid therapy before and during the pre-assessment period increases the likelihood of being classified as non-responders.

Method

The patients were divided into those who showed a response to anti-TNF at 6 months (DAS28 dropped by ≥1.2) (responders) and those who did not (non-responders). These groups were compared for age, sex, disease duration, DAS28 at the two pre-assessments 1 month apart and at baseline and the differences in these DAS28s, type of anti-TNF used, baseline dose of MTX and dose at 6 months and the changes in these doses. The practice at Derbyshire Royal Infirmary is for specialist nurses to perform two DAS28 pre-assessments a month apart, followed by a further baseline assessment being recorded soon after this at drug initiation. Comparisons were made using chi-squared, t-tests and Mann–Whitney U-tests where appropriate.

In order to establish whether patients who had steroids before and during the pre-assessment period were more likely to be classified as non-responders to anti-TNF drugs, patient records were examined to identify as to which patients had either IM, IA or oral steroids administered or increased within the 3 months period before the baseline DAS28. This data was evaluated to determine whether the administration of steroids could affect a patient’s chances of subsequently being classified as responder or non-responder to anti-TNF. The time interval between steroid administration and the date when the baseline DAS was taken were also calculated and compared between the responders and non-responders groups. Correlations were made between the change in DAS28 from the first pre-assessment to baseline, and the number of days before baseline that steroids were administered (expressed as Pearson correlation coefficients).

All calculations were performed using SPSS12.0 for Windows (Chicago, IL, USA). The study was registered with the Audit Committee of the Derbyshire Royal Infirmary.

Results

Data was available on 256 patients. The majority of patients were on etanercept 185 (73%) with 46 patients (18%) on infliximab and 24 patients on adalimumab (9%). Of the patients, 212 (82.8%) were classified as responders at 6-month assessments and 44 (17.2%) were not. There were no significant differences in the sex or disease duration of responders and non-responders, though non-responders had a tendency to be older (Table 1). Furthermore, there were no significant differences between the groups for baseline MTX (for responders median dose 0 mg, 64.9% of patients on no MTX, for non-responders 5 mg and 47.5%, respectively), or changes in the drug at 6 months (for responders median dose 0 mg, 63.8% of patients on no MTX, for non-responders 0 mg and 54.8%, respectively, Mann–Whitney U-tests for all comparisons, P > 0.05).

Table 2 shows the comparisons of DAS28 at pre-assessments and baseline for the responders and non-responders. Although the first pre-assessment DAS28 was not significantly different (mean score 6.8 for responder and 6.6 for non-responders), the second pre-assessment score was lower in the non-responders (7.1 for responder vs 6.7 for non-responders; mean difference 0.4; 95% CI 0.0, 0.8; P = 0.04). Baseline DAS28 was also significantly lower in the non-responders (6.3 vs 7.2; mean difference 0.8; 95% CI 0.5, 1.2; P < 0.001). Comparing the differences in DAS28 from the first pre-assessment to baseline, the responders had increased by 0.4, and the non-responders had decreased by 0.4, (mean difference 0.8; 95% CI 0.5, 1.1; P < 0.001). If the first pre-assessment score had been taken as the baseline DAS28, then 9.4% of responders would be re-classified as non-responders, and 31.8% of non-responders would be re-classified as responders.

The proportion of non-responders for adalimumab, etanercept and infliximab was 29, 11 and 35%, respectively (P = 0.008). Of the 212 responders, 72 (34%) and of the 44 non-responders 18 (41%) had received IM, IA or oral steroids administered or increased within the 3-month period before baseline DAS28. This difference was not significant (P = 0.38). Furthermore, there was no significant difference between the two groups in the number of days before baseline that the steroids were administered (mean number of days 51.8 for responder and 51.6 for non-responders; P = 0.966) There was also no correlation between the change in DAS28 from the first pre-assessment to baseline, and the number of days before baseline that steroids were administered (r_p = −0.141; P = 0.72). Within the group of non-responders there was no significant difference in the change in DAS28 from the first pre-assessment to baseline between those patients who had received steroids within the 3-month period before baseline DAS28 (18 out of 44 patients; mean decrease in DAS28 of 0.5) and those patients who had not (mean decrease in DAS28 of 0.3; t-test mean difference 0.2; 95% CI -0.3, 0.8; P = 0.39).

Discussion

The current NICE guidelines for the continuation of anti-TNF therapy require a DAS28 improvement of >1.2 from baseline determined at 6 months after commencement and every 6 months thereafter [10]. Hence, the DAS28 that is counted as the baseline is now more important than ever. It has become the reference value against which all the subsequent assessment of an individual patient’s response to anti-TNF is measured. Patients with lower baseline DAS28 are likely to get less of a drop in their DAS28 [8]. Although the majority of patients are classified as responders at 6 months according to the NICE guidelines, a significant
proportion are not. Our retrospective study shows that the baseline DAS28 is critical to classifying responder and non-responders at 6-month assessment. Non-responders are more likely to have a lower DAS28 at baseline, and a drop in DAS28 from first pre-assessment to baseline. In Derby, the two pre-assessment and the baseline DAS28s are usually taken within 6 weeks of each other. We have found that replacing the baseline score with the first pre-assessment DAS28 led to a significant re-classification of responders and non-responders.

At the time of the first pre-assessment, many patients may get significant temporary benefit from steroid therapy in the month that the NICE guidelines dictate that they must wait before being eligible to go onto anti-TNF. Not infrequently, steroid therapy is withheld from these patients before and during the pre-assessment period to optimize their chance of fulfilling the NICE eligibility criteria for anti-TNF therapy. Because the non-responders had a tendency for their DAS28 to decrease from the first pre-assessment to baseline, we were concerned that this might reflect a greater use of steroids around the pre-assessment period for this group of patients. However, our analysis shows no significant difference in those subsequently classified as anti-TNF responders and non-responders for:

(i) the proportion of patients receiving IM, IA or oral steroids within the 3-month period before baseline DAS28;
(ii) the number of days prior to baseline DAS28 that the steroids were administered; and
(iii) no correlation between the change in DAS28 from the first pre-assessment to baseline, and the number of days before baseline that steroids were administered.

Within the non-responders there was no significant difference in the change in DAS28 from the first pre-assessment to baseline between those patients who had received steroids within the 3-month period before baseline DAS28 and those who did not. Taken together, our data suggests that withholding symptom-relieving steroid therapy in the months prior to anti-TNF treatment does not increase the chances of being classified as non-responders, and therefore there is no reason to deny steroids to patients around this pre-assessment period.

We have argued elsewhere that pre-assessments taken 1 month apart are an inappropriate delay in starting anti-TNF therapy, because there are very high correlations among the pre-assessment scores, and patients with a DAS28 > 5.1 at first pre-assessment hardly ever have a DAS28 that falls below this level in subsequent pre-assessments [11]. This is not to say that we are arguing that a single DAS28 pre-assessment is satisfactory. Because of the fluctuating nature of disease activity in RA, we would suggest that several pre-assessment DAS28s are performed to determine patient eligibility (perhaps at different times of the day given the diurnal variation of the disease), but there is no rationale behind these being a month apart. It would seem most appropriate to take the highest of the pre-assessment DAS28s, because that which is accepted as the baseline score makes a big difference to whether or not a patient is subsequently classified as a non-responder. It is our hope that these recommendations will be incorporated into subsequent BSR guidelines, and ultimately into NICE guidelines.

<table>
<thead>
<tr>
<th>Characteristics of anti-TNF non responders at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline DAS28 is critical in classifying responders and non-responders at 6-month assessment.</td>
</tr>
<tr>
<td>Non-responders are more likely to have a lower DAS28 at baseline, and a drop from first pre-assessment to baseline.</td>
</tr>
<tr>
<td>There is no evidence to suggest that withholding steroid therapy in the months prior to anti-TNF treatment increases the chances of being classified as a non-responder.</td>
</tr>
</tbody>
</table>

Acknowledgements

Funding: The Department of Rheumatology at Derbyshire Royal Infirmary has received sponsorship from Wyeth, Abbott and Schering Plough Pharmaceuticals for support of clinical meetings, and unrestricted grants from Wyeth and Schering Plough to support an anti-TNF audit clerk and research nurse.

Disclosure statement: K.G. sits on an advisory board for Schering Plough, and has received honoraria for talks at symposia sponsored by Wyeth and Abbott. C.D. previously sat on an advisory board for Schering Plough and received honoraria for talks at symposia sponsored by Wyeth and Abbott. All other authors have declared no conflicts of interest.

References