Concise Report

Is pre-assessment for anti-TNF therapy in RA necessary in the UK? Analysis of DAS28 in six centres

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Objectives. National Institute for Health and Clinical Excellence (NICE) guidelines for anti-tumour necrosis factor (TNF) in rheumatoid arthritis (RA) state that two pre-assessments of Disease Activity Score (DAS28) should be performed a month apart. We performed a retrospective audit of data from six centres to determine the stability of DAS28 between assessments, and the proportion of patients still satisfying eligibility criteria at baseline.

Methods. All RA patients assessed for anti-TNF from six centres had their pre-assessment DAS28 (DAS-1) compared with their baseline DAS28 (DAS0) using paired t-tests, and a similar analysis for the components of the DAS28. Patients who were no longer eligible for anti-TNF at DAS0 were noted.

Results. Six hundred and seventy-nine RA patients showed no significant change in the DAS28, with a mean DAS-1 of 6.74 and DAS0 of 6.73. (P = 0.86). Of the patients, 97.2% fulfilled the UK eligibility criteria at DAS0. Comparison of the individual components of the DAS28 between the two pre-assessment dates showed that there was no significant difference between either the numbers of swollen joints or the erythrocyte sedimentation rate (ESR), but there was a significant increase in the numbers of tender joints of 1.41 (P < 0.001) and in the visual analogue scale (VAS) of 4.22 (P < 0.001).

Discussion. The overwhelming majority of patients who fulfil eligibility criteria for anti-TNF drugs 1 month prior to baseline also fulfil the criteria at baseline. There is no significant change in the DAS28 over the month waiting to go onto anti-TNF therapy. A single assessment of the DAS28 would suffice to enable patients to go on to anti-TNF treatment.

Introduction

In 2001, the British Society for Rheumatology (BSR) first issued guidelines for the use of anti-tumour necrosis factor (TNF) agents for the treatment of rheumatoid arthritis (RA) [1], recommending that patients should have a Disease Activity Score (DAS28) of greater than 5.1 units on at least two occasions, 1 month apart, prior to commencing treatment. This was to try to ensure that the drugs were reserved for patients with persistent active disease. According to the European League Against Rheumatism (EULAR) criteria, a DAS28 of 3.7 is the cut off for high levels of disease activity [2], so the figure of 5.1 suggests severe disease.

The National Institute for Health and Clinical Excellence (NICE) accepted the BSR guidelines and published them unchanged as a Technology Appraisal in 2003 [3]. The BSR guidelines were updated in February 2005 [4], and in the absence of evidence to change the eligibility criteria, they remained unchanged. In November 2006, NICE issued a Final Appraisal Determination (still the subject of appeal at the time of writing) on the use of the anti-TNF agents adalimumab, etanercept and infliximab for the treatment of RA [5]. These guidelines also proposed the same pre-assessment criteria. A similar approach with two separate pre-assessments has been advocated to ensure persistent active disease in the BSR ankylosing spondylitis anti-TNF guidelines [6]. It is interesting to note that both the NICE and BSR psoriatic arthritis anti-TNF guidelines [7, 8] require only a single baseline assessment of disease activity.

For many patients this pre-assessment month can appear to be an unnecessarily cruel delay of the inevitable introduction of the drug, particularly if temporary symptom-relieving interventions, such as steroid injections, are withheld over this month, in order to avoid a short-term improvement that may result in failure to meet the eligibility criteria at the second assessment date. Building on a previous study that was conducted in three centres in 2006 [9], we performed a retrospective audit of pre-assessment DAS in patients screened for anti-TNF therapy in six rheumatology departments in UK.

Objectives

The aims of the study were to determine:

(i) whether there were any differences in DAS28 between the two dates at least 1 month apart, prior to the introduction of anti-TNF;
(ii) whether there were any differences in the components of the DAS28 between the two pre-assessment dates; and
(iii) what proportion of patients continued to have a DAS28 of more than 5.1 at the second assessment, thus fulfilling the UK NICE and BSR eligibility criteria.

Method

Pre-assessment DAS28 data, 1 month apart, were collected on 712 RA patients intending to commence treatment with anti-TNF therapy [Birmingham (101 patients), Cannock (40 patients), Derby (273 patients), Manchester (82 patients), Newcastle (130 patients)]. Analysis of DAS28 in six centres

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patients) and Portsmouth (86 patients). All patients fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA, in keeping with BSR and NICE guidelines [3, 4].

All patients had their first pre-assessment DAS28 (DAS-1) compared with their subsequent baseline DAS28 (DAS0) using a paired t-test. We also performed paired t-tests on the components of the DAS28, to compare the values at the two pre-assessment dates. We then performed correlation coefficients for the same variables and determined how many patients who had a DAS-1 of greater than 5.1 subsequently failed the eligibility criteria for anti-TNF therapy by having a DAS0 of less than 5.1.

Results
Of the 712 patients, 33 were excluded as follows: 12 had a DAS-1 of less than 5.1 so would be ineligible for treatment with anti-TNF, 16 had no baseline DAS0 recorded, and five had no erythrocyte sedimentation rate (ESR) data available for one or both dates, so a calculation of DAS was not possible.

The remaining 679 RA patients had a DAS-1 of greater than 5.1. Figure 1 shows a plot of DAS-1 against DAS0. Of the patients, 49.8% had deteriorated in their DAS28 over the month. However, there was no significant change in the overall mean DAS28, with a mean DAS-1 of 6.74 and DAS0 of 6.73, mean difference 0.01 [95% confidence interval (CI) −0.06 to 0.07, t = 0.18, P = 0.86]. The correlation coefficient was 0.53, P < 0.001. Nineteen patients had a DAS0 of less than 5.1. Therefore, 97.2% fulfilled the UK eligibility criteria at DAS0.

Comparison of the individual components of the DAS28 between the two pre-assessment dates showed that there was no significant difference between either the numbers of swollen joints or the ESR, as detailed in Table 1. There was, however, a significant increase in the numbers of tender joints of 1.41 (95% CI 0.74–2.09, t = 4.11, P < 0.001) and a significant increase in the visual analogue scale (VAS) of 4.22 (95% CI 2.56–5.88, t = 4.99, P < 0.001).

Discussion
Our results in a much larger data set support the conclusions in the previous study [9]:

(i) The overwhelming majority of patients who fulfil eligibility criteria to go on to anti-TNF drugs at 1 month prior to baseline also fulfil the criteria at baseline.

(ii) Patients do not show any significant change in their overall DAS28 over the month that they wait to go onto anti-TNF therapy.

(iii) Two of the components of the DAS28 do show a significant worsening over the month. These are both patient-determined variables and there is a possibility, therefore, that this reflects a lower pain threshold for tender joints and a more negative view of overall health and well-being amongst patients potentially eligible for anti-TNF therapy, in an attempt to ensure eligibility for the drug. The fact that the objective criteria of ESR and experienced-nurse-determined swollen joint count remained the same over the month, however, suggests that this would not be a major factor contributing to the maintenance of the DAS28 above 5.1.

The DAS28 has problems. A study of DAS28 in RA suggested that there is too much inherent variability in the DAS to recommend it as a sole determinant of RA activity for clinical or regulatory purposes [10]. The DAS28 is based on an objective measures (ESR), a practitioner-determined variable (the number of swollen joints) and two patient-determined variables (the number of tender joints and the VAS) [11]. Having said that, Leeb et al. [12] found that there was a high correlation between all the DAS components, both objective and subjective, in their RA patients. An analysis of 49 UK patients [13] found that the swollen joint count was the single most important predictor of response based on the DAS28 composite score and patient global assessment. The authors went on to propose that additional weight be given to the number of swollen joints when assessing patients for biological therapy, since this correlates far better with clinical response than, for example, DAS28 alone.

In comparison with many other guidelines around the world, the UK’s guidelines are already a lot more restrictive. A recently updated consensus statement on biological treatments, by national experts from the US and Europe [14], continues to advise that biological treatments should be considered after the failure of one DMARD in patients with active RA, which is undefined. In the Irish Rheumatology Society’s guidelines for prescribing TNF-α blockers in adults with RA [15], it is stipulated that a patient should have persistent, active RA to be eligible for anti-TNF therapy, but again ‘active RA’ is undefined. It does suggest that pre-assessments of disease severity should be made on two occasions at least a month apart, but this is not mandatory. The ACR guidelines for the management of RA [16] suggest that patients should be eligible for anti-TNF therapy if treatment with methotrexate is contra-indicated or fails to achieve satisfactory disease control. The guidelines in Holland permit consideration of anti-TNF treatment following failure of one DMARD and a DAS28 greater than 3.2 [17]. In Italy, patients need a DAS28 greater than 5.1 to qualify for anti-TNF, but the assessment need only be performed on one occasion [18]. In comparison with other countries, the NICE guidelines originally proposed by the BSR appear unduly prohibitive. It is also inconsistent to only require a single measurement of disease activity in the NICE guidelines for anti-TNF therapy in psoriatic arthritis [7, 8]. The present study sought to determine whether there was a justification for maintaining the current pre-assessment regime for

<table>
<thead>
<tr>
<th>DAS-1</th>
<th>DAS0</th>
<th>Mean difference</th>
<th>95% CI (lower)</th>
<th>95% CI (upper)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28</td>
<td>6.74</td>
<td>6.73</td>
<td>0.01</td>
<td>−0.06</td>
<td>0.07</td>
<td>0.18</td>
</tr>
<tr>
<td>Number of tender joints (max. 28)</td>
<td>17.05</td>
<td>18.47</td>
<td>1.41</td>
<td>−2.09</td>
<td>−0.74</td>
<td>−4.11</td>
</tr>
<tr>
<td>Number of swollen joints (max. 28)</td>
<td>12.25</td>
<td>12.46</td>
<td>0.21</td>
<td>−0.70</td>
<td>0.29</td>
<td>−0.83</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>48.29</td>
<td>47.17</td>
<td>1.12</td>
<td>−0.70</td>
<td>2.95</td>
<td>1.21</td>
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<tr>
<td>VAS (0–100 mm)</td>
<td>70.65</td>
<td>74.87</td>
<td>−4.22</td>
<td>−5.88</td>
<td>−2.56</td>
<td>−4.99</td>
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anti-TNF in RA. Other studies will have to address whether DAS28 should be replaced, modified, or whether a number of measures of disease activity should be used in order to assess eligibility for anti-TNF therapy [19].

Conclusion
In view of the proven stability over time of the overall DAS28 and the individual components of this scoring method, we feel that a single assessment of the DAS28 would suffice to enable patients to go on to anti-TNF treatment. We feel that the UK NICE guidelines should be changed to a single assessment of disease activity. This would reduce the delay in treatment being commenced in UK patients who already have stricter eligibility criteria than other countries and who, by having to fail to respond to at least two conventional disease-modifying drugs, will have severe, resistant and established disease.

Rheumatology key messages
- Of the patients, 97.2% fulfil eligibility criteria at both baseline and 1 month prior.
- There is no significant change in DAS28 over the pre-assessment month.
- A single assessment of DAS28 would suffice.

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References
5. NICE Technology Appraisal - Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (final appraisal determination) www.nice.org.uk.