Arthritis and Musculoskeletal Alliance

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Dear Dr Longson,

Response to Appraisal Consultation Document: adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (review of guidance no.36)

Thank you for the opportunity to comment on the Appraisal Consultation Document. This response has been developed by a working group that included representatives from the following organisations; Arthritis Care; Arthritis Research Campaign; British Health Professionals in Rheumatology; the British Society for Rheumatology; the National Rheumatoid Arthritis Society; the Primary Care Rheumatology Society; and the Royal College of Nursing Rheumatology Forum, under the auspices of the Arthritis and Musculoskeletal Alliance. Our collective response is based on the comments made by members of this group.

We are content with many of the conclusions reached in the ACD, although emerging data suggest that these drugs may be even more effective when used very early in the disease process (e.g. after only methotrexate or one other DMARD) and it is expected that future applications to NICE will include this indication in keeping with the current usage in other European and North American countries. Furthermore the current British Society for Rheumatology Guidelines suggest that there could be circumstances under which the therapies should be used early in the course of the disease.

However we have a number of outstanding concerns that we believe should be addressed. These concerns are around two main subjects:

1. We strongly believe that the sequential use of TNF-α inhibitors on the grounds of lack of efficacy should be allowed.
2. We question the DAS criteria outlined for stopping the use of TNF-α inhibitors (paragraphs thirteen to sixteen)

We have responded under the general headings outlined in your letter of the 26th of January, namely:

- Consideration of the relevant evidence
- Appropriateness of the summaries of clinical and cost effectiveness as interpretations of the evidence and the preliminary views on the resource impact and implications for the NHS

- Suitability of provisional recommendations of the ACD as a sound basis for preparation of guidance to the NHS

Consideration of the relevant evidence

1. We do not consider that all of the relevant evidence has been taken into account regarding both sequential use of TNF-α inhibitors and the DAS criteria for stopping the therapy.

Sequential use of TNF-α inhibitors, where a previous inhibitor has failed

ACD Paragraph 4.3.14 *The Committee heard that there is currently limited evidence related to the sequential use of the TNF-α inhibitors ….. The Committee therefore considered that there was as yet insufficient evidence on which to base recommendations for sequential use outside the context of clinical studies….*

2. We strongly disagree with this statement. There are major pharmacological differences between the currently licensed drugs, which may explain variability in clinical response between different patients. There are at least 10 published studies to support the use of sequential treatment following failure to respond to the first TNF-α inhibitor. In addition, there are a number of other large studies that have been presented at learned societies that are currently only available in abstract form. We have decided not to include these in this review except the data from the BSR biologics register.

3. TNF-α inhibitors cannot be regarded as interchangeable because of differences in their structures, actions and pharmacokinetics (reviewed in Scallon 2002 et al., Haroui 2004 and Mpofu et al. 2005). This provides a plausible explanation for the observation that many patients who have failed to respond to one TNF-α inhibitor will respond to a different agent.

- **a.** Infliximab is a humanised mouse monoclonal antibody; adalimumab a fully human monoclonal antibody, and etanercept a construct of two p75 TNF-α receptors coupled to the Fc portion of a human monoclonal antibody.
- **b.** Etanercept binds both TNF-α and TNF-β (lymphotoxin), whereas infliximab and adalimumab bind only TNF-α.
- **c.** Infliximab binds both inactive monomeric TNF and active trimeric TNF whereas etanercept binds only active trimeric TNF.
- **d.** Infliximab forms stable complexes with TNF-α whereas etanercept forms relatively unstable complexes which can dissociate, resulting in the release of bologically active TNF-α.
- **e.** Infliximab, but not etanercept, will form stable complexes with membrane-bound TNF-α.
- **f.** Infliximab and adalimumab are IgG1 antibodies which bind complement, unlike etanercept, and so can lyse cells which express TNF-α on their surface.
- **g.** The pharmacokinetics of the agents differ: infliximab infusions result in a high peak level which declines to very low or undetectable levels at 6-8 weeks. By contrast twice weekly dosing with etanercept achieves more sustained levels but does not achieve a high peak level as seen with infliximab.

h. Infliximab is effective in Crohn's disease but etanercept does not appear to be so.

i. Conversley etanercept is effective in juvenile idiopathic arthritis but infliximab does not appear to be so.

In view of these differences, it is important to evaluate the results of treatment with different agents when one has failed. The available data is reviewed briefly below.

Single centre reports

4. One of the earliest published studies, by Brocq and colleagues, reported an excellent response in 8 of 14 patients who were retreated with a second TNF-α inhibitor after failure of the first drug, although only 6 patients had initially failed from lack of efficacy.

5. Hansen and colleagues compared the result of infliximab treatment in 73 patients without prior TNF inhibition with 20 patients who were switched from etanercept to infliximab because of treatment failure. All outcome measures improved in both groups and they concluded that previous lack of efficacy with etanercept did not predict a lack of efficacy with infliximab although the 'switchers' were receiving a higher dose of infliximab. Conversely, Sanmarti and colleagues found a good response in 10 out of 12 patients who switched to etanercept after failure to respond to infliximab with a highly significant improvement in DAS score.

6. Haraoui and colleagues undertook a prospective open study evaluating the response to etanercept in 25 patients who failed treatment with infliximab. They found at least an ACR 20 response in 64% of patients after 12 weeks of treatment and a reduction in HAQ score $\geq$ 0.22. Similarly, Buch and colleagues found a 68% ACR 20 and 51% ACR50 response after 12 weeks treatment of etanercept in patients who failed to respond to infliximab. In 29 patients who had failed either infliximab or etanercept and then treated with the other drug, Ang and Helfgott also concluded that patients who failed one drug from inefficacy may respond to the other.

7. van Vollenhoven and colleagues have reported separate analyses of response following re-treatment with either infliximab or etanercept after failure of the other drug, or treatment with adalimumab following failure with either of the other TNF-α inhibitors (Wick et al 2004). In the first analysis, they found a reduction in DAS from 4.8 to 3.6 after secondary treatment with infliximab in 18 patients. They also found a similar response in efficacy from etanercept in 13 patients who had stopped infliximab for toxicity. In the second analysis they found an ACR 20 response of between 70% and 78% from adalimumab in those who had failure of response with the primary TNF-α inhibitor. After 6 months treatment with adalimumab, the reduction in DAS scores was 5.2 to 4.2 in 27 patients after infliximab failure and 5.7 to 4.1 in 9 patients after etanercept failure. This response was compared with 26 patients who had a reduction in DAS of 5.6 to 3.5 from adalimumab as the primary biologic.

8. Nikas and colleagues have recently reported the outcome of 24 patients treated with adalimumab who had discontinued treatment with infliximab, 9 because of lack of efficacy. They compared the outcome with 25 patients treated with adalimumab as the first TNF-α inhibitor. Of those who were re-treated because of lack of efficacy from infliximab, 89% achieved ACR 20, 56% ACR 50 and 33% ACR 70, compared with 76%, 56% and 36% respectively in the primary treatment group. There was also no significant difference in DAS scores between the 2 groups.

National databases

United Kingdom

9. Hyrich and colleagues (2005) have reported the results of switching from one TNF-α inhibitor to another in the BSR biologics register. They had recruited 6,318 patients with rheumatoid arthritis who started TNF-α inhibitor between October 2001 and July 2004 and had been followed to January 2005; 950 (15%) discontinued their first TNF-α inhibitor following an adverse event and 796 (13%) for lack of response. Of these, 446 (47%) and 496 (62%) respectively, switched to a second agent. The non-response rate to the second agent was 16% in those non-responding to the first and 9% in those who experienced an adverse event to the first. Similarly the cumulative adverse event proportion to the second agent was 23% in those patients with an adverse event to the first drug and only 9% in those who discontinued the first drug due to non-response. The authors calculated that there was an increased risk of non-response with the second drug if the patient had not responded to the first drug but the risk of an adverse event occurring on a second TNF-α inhibitor in a patient who has discontinued a previous TNF-α inhibitor for lack of effect is not increased. In contrast, if the reason for a switch was an adverse event, they calculated the likelihood of recurrent adverse event to be about two to three fold. However, they concluded that following failure to a first TNF-α inhibitor the large majority of patients may respond to a second one. As noted these data have only been published in abstract form to date but longer term data and data on HAQ and SF-36 are being analysed prior to publication but cannot be cited here due to the deadline set for this submission.

Spain

10. The Spanish Society of Rheumatology initiated a biologics register in February 2000. Gomez-Reino and Carmona (2006) have published the results of switching TNF-α inhibitors in 488 patients from a total of 4,706 registered patients (3,200 with RA). Continuation of each drug when used for primary treatment was 88% for etanercept, 87% for adalimumab and 81% for infliximab. Eighty-three per cent of the RA patients completed one year's treatment with their first TNF-α inhibitor compared with 79% of the 385 who switched to a second. When the primary drug was stopped because of lack of efficacy, the rate of discontinuation of the second drug for lack of efficacy per 100 patient years exposed was 9.3 for etanercept, 12.5 for adalimumab and 38.5 for infliximab (compared with 3.6, 3.2 and 4.7 respectively when administered as the primary drug). The rates of discontinuation for adverse events when used first or second were 3.8 and 6.1 for etanercept, 7.2 and 12.5 for adalimumab and 6.5 and 32.7% for infliximab respectively. Overall, when the drugs were used as secondary treatment, 76% continued etanercept and 67% adalimumab, compared with 34% for infliximab. The authors considered the results for infliximab might have been confounded by this treatment having been initiated 40 and 50 months prior to the other two compounds but were otherwise unable to explain the differences.

Conclusions relating to sequential treatment

11. There are pharmacological reasons why there may be differences in both efficacy and toxicity between the TNF-α inhibitors. Considerable data is available evaluating the response of patients who have switched TNF-α inhibitors because of a lack of efficacy from the primary drug. The data indicates that there is a significant clinical response in the majority of patients. Although the magnitude of response is reduced compared with primary treatment responses, the difference in response rates between primary and secondary treatment is small and the majority of patients is likely to respond.

12. Withholding treatment with a second drug from a patient with active rheumatoid arthritis who has failed treatment with their first TNF-α inhibitor is likely to deny the patient their only option for effective treatment and lead to increased pain, joint destruction and disability. We consider it wholly inappropriate to deny potentially effective treatment for this group of patients. We urge the committee to re-evaluate this statement and to recommend a therapeutic trial with a second TNF-α inhibitor if treatment is withdrawn as a result of either adverse effects or lack of efficacy from the first drug. The data indicates that those who respond have measurable improvement after 12 weeks of treatment. If there is an inadequate response, as defined for initial treatment, treatment should be withdrawn.

DAS criteria for stopping therapy

ACD Paragraph 1.2

Treatment with TNF-α inhibitors should be withdrawn if there is an inadequate response at 3 months or in the event of severe drug-related toxicity. Inadequate response is defined as a lack of improvement by at least 1.2 points in the DAS28.

13. This fails to take into account those patients who have managed to decrease or stop other medication such as steroids. This is a worthwhile clinical outcome that might not be reflected in a large drop in DAS scores. Such patients should be given a further 3 month trial. This was recommended in the updated BSR guidelines [Ledingham and Deighton, 2005].

14. We also wish to highlight that the BSR guidelines have over-simplified EULAR response criteria. In future, if DAS is retained in eligibility criteria, we would seek to align the BSR guidelines and EULAR response criteria more closely.

ACD Paragraph 1.3

Treatment should be monitored at regular intervals. Over the first 18 months, DAS28 should be assessed at 6, 12 and 18 months. Treatment should be withdrawn if response is not maintained, defined as evidence of clinical deterioration (DAS28 score increasing by more than 0.6) at consecutive assessments.

15. It would be inappropriate to withdraw anti-TNF on the basis of consecutive assessments of DAS28. The most equitable approach would be to compare assessments at 6, 12 and 18 months with the baseline DAS28, as initial DAS might drop substantially immediately after the introduction of TNF-α inhibitor and then plateau to fluctuate around a stable level. A rise of 0.6 on consecutive scores might be small in comparison with the initial substantial decrease in DAS28 scores often seen after the introduction of anti-TNF. For example if a baseline DAS28 was 6.9, a 6 month DAS28 3.2 and a 12 month assessment 3.9, it would be perverse to stop the anti-TNF because of this rise in DAS, because the patient remains so much better than they had been prior to the introduction of the drug. If on the other hand the DAS rises within 0.6 of the baseline score, this would be much more suggestive of loss of efficacy

16. It is also inappropriate to rely on a single assessment. Those patients who have a DAS28 that increases by more than 0.6 might simply be having a flare

up on the day when they are assessed, and this might not be a representative assessment of their disease control over the previous 6 months. All patients have to demonstrate a stable DAS28 above 5.1 on two separate occasions to be eligible to go onto TNF-α inhibitors. It would be appropriate for patients whose 6 monthly assessment suggests that they are losing response should be given the opportunity for a second assessment within 1 month. .

Appropriateness of the summaries of clinical and cost effectiveness as interpretations of the evidence and the preliminary views on the resource impact and implications for the NHS

17. As indicated by our response to question (1) we do *not* consider that the ACD represents a reasonable interpretation of the clinical effectiveness of sequential use of TNF-α inhibitors, or that the criteria for assessment of loss of response at 6, 12 and 18 months are fair as currently stated.

Suitability of the provisional recommendations of the ACD as a sound basis for preparation of guidance to the NHS

18. As indicated by our response to question (1) we do *not* consider the recommendations sound and hence do not consider them suitable as a basis for the preparation of guidance to the NHS.

We hope that this information is given due consideration and is of assistance to NICE in its decision making process. If you have any queries or require further detail or clarification about any of the comments enclosed do contact us.

Yours sincerely,




On behalf of:
Arthritis Care
Arthritis Research Campaign
British Health Professionals in Rheumatology
British Society for Rheumatology
National Rheumatoid Arthritis Society
Primary Care Rheumatology Society
Royal College of Nursing Rheumatology Forum
under the auspices of the **Arthritis and Musculoskeletal Alliance**

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