Dr Carole Longson,
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27th February 2008

Dear Dr Longson,

Health Technology Appraisal
Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis

Thank you for asking us to comment on these documents.

'The sequential use of TNF-α Inhibitors.'
Update to a report by the Decision Support Unit (Allan Wailoo, School of Health and Related Research, University of Sheffield).

Overall the Decision Support Unit (DSU) has given a fair review of the available evidence on TNF inhibitor switching. DSU conclude that 70% of people switching TNFα-inhibitor for lack of efficacy may have good or moderate EULAR response (Table 6). For individual drugs 23-66% of people switching to etanercept have ACR50 response or 16-67% a moderate EULAR response; for adalimumab 25-56% ACR50 response and 35-71% EULAR moderate response; for infliximab the numbers are very small. There are few studies on changes in HAQ, but for etanercept the range of decreases is -0.41 & -0.45, for adalimumab -0.31 to -0.55, and for infliximab -0.13. From a patient perspective most of these drops in HAQ would make a significant difference to the quality of their lives, with a HAQ drop of 0.22 being recognized as the minimal clinically important difference.

'The effectiveness of non biologic DMARDs after Anti TNF α Inhibitor failure.'
Decision Support Unit (Allan Wailoo, Jonathan Tosh, School of Health and Related Research, University of Sheffield).

The fact that people in BSRBR have on average long disease duration and have used many DMARDs is well accepted and this is likely to have an adverse effect on their ability to respond to a TNF-inhibitor, whether used first or second.

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Important data from the BSRBR abstract from EULAR 2007, (Hyrich K et al, Effect of switching to a second anti-TNF therapy on HAQ response in rheumatoid arthritis patients with lack of response to their first anti-TNF therapy: results form the BSRBR. Ann Rheum Dis 2007;66(suppl II):173) has not been considered. To summarise, the evidence found that patients who stopped anti-TNF and did not go onto another biologic had no change in their HAQ over one year. This group would have returned to non-biologic DMARDs, or pain-killers or some other palliative care, and showed no change. This is important because it reflects real world clinical practice, with no placebo effect as seen in clinical trials. Patients who do not go onto another biological therapy have a HAQ that remains static over a year. This is in marked contrast to the improvements in HAQ in patients going onto a second anti-TNF, as summarized in the DSU's first paper above.

It is also important to note the data showing that people on DMARDs in placebo arms of abatacept (Genovese) and Ritiuximab (Cohen) trials showed only a small HAQ improvement of 0.1 at 6 months.

With regard to the Brennan study, the study looked at EULAR response and not HAQ. The analysis does not look specifically at patients who have previously failed a biologic.

'Further cost-effectiveness analysis of sequential TNF inhibitors for rheumatoid arthritis patients.'
(Pelham Barton, West Midlands Health Technology Assessment Collaboration).

The modelling with HAQ estimates made by DSU from clinical trials certainly reduces ICERs considerably compared with the original values used in the BRAM model. When BRAM models the cost-effectiveness of the use of the 2nd TNF inhibitor after failure of the first using BSRBR data, the ICERs are above usually accepted NICE cost-effectiveness thresholds. Using HAQ response estimates made by DSU from clinical trials rates gives ICERs closer to the threshold at £31k-39k. However, as the DSU indicated that 70% of patients had a good or moderate EULAR response to a second TNF inhibitor, this raises concerns regarding the reliability of the BRAM model. One concern relating to the model is described on the first page of the report. On page 1, point 2 it states that a multiplicative model has been chosen. This appears to reflect percentage rather than actual improvement in HAQ. An example is given of a HAQ reducing with treatment from 2.00 to 1.00 and from 0.50 to 0.25 being equal response. We believe this to be flawed. The HAQ is a non linear scale. Changes in high scores may be more important for quality of life than changes in low scores e.g. a reduction of a score from 'unable' to walk to 'much difficulty', is the same numerically as from 'much difficulty' to 'some difficulty', but influences quality of life differently. In addition, the magnitude of change is important. A reduction from 2.00 to 1.00 is a clinically significant improvement. A reduction fro 0.5 to 0.25 may be more difficult to detect clinically. We are concerned that this model may therefore underestimate the QALYs from TNF treatment. Even if there is only a small underestimate of the benefit, it is likely that this would reduce the ICERs from 31K-39K to below the 30k threshold.

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When a 2nd TNF inhibitor is compared with Rituximab, ICERs are high for BSRSR data (£56k-75k), but when HAQ estimates from the DSU clinical trials data are used, they are closer to the cost-effective threshold (£31k-51k). Using higher doses of infliximab takes it above NICE thresholds as one would expect (>£40k). It should be noted that RA that is seronegative for rheumatoid factor shows much poorer responses to rituximab than seropositive disease, and it would have been extremely helpful if this variable could have been included in the comparative models. Rheumatoid factor status does not predict response to anti-TNF (Hyrich KL et al. Predictors of response to anti-TNFα therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology 2006;45:1558-65), but it is important in predicting response to rituximab. Seronegative RA may be more cost-effectively treated by a second anti-TNF than by rituximab.

ON page 7, the table shows the improvement in HAQ required for use of a second TNF-inhibitor to be cost-effective at either £20k or £30k threshold after the first has failed for inefficacy. A HAQ improvement of 0.3 would make it cost-effective at £30k. This has been achieved or exceeded in most of the studies. The £20k threshold is not achievable based on the DSU data.

The report by the DSU supports our previous response, indicating that there is a moderate or good clinical response in the majority of patients treated with a second TNF inhibitor after having a poor response to the first TNF inhibitor. It is therefore appropriate to recommend such treatment in patients with active disease when other therapeutic options are limited. We consider that providing the guidance indicates that treatment is only continued when there is an identifiable clinical response, it would inappropriate not to recommend such treatment. We have also argued that due to potential underestimation of benefit for technical reasons in the BRAM, that the failure of that model not to demonstrate ICERs below the 30k threshold should not be used to deny patients effective treatment. We also need to highlight the fact that the people with RA on whom data has been collected so far in BSRBR represent people with late and extensively treated RA, having failed a median of four DMARDs, and with a mean of 14 years disease duration. They therefore have less capacity to achieve a good HAQ response to a first, let alone 2nd TNF-inhibitor, and so the responses observed are less than can be achieved in earlier disease, as illustrated by the clinical trial data.

Yours sincerely,

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