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20th May 2008

ARMA Response to Sequential Use of Anti-TNF ACD

We thank NICE for giving us the opportunity to comment on this Appraisal Consultant Document (ACD).

i). Do you consider that all of the relevant evidence has been taken into account?

We feel that the committee has failed to take all of the evidence into account on three counts:

1. Returning to conventional disease modifying drugs following the failure of the first anti-TNF therapy.
    a. Page 5 of the report from Abbott shows data from the British Rheumatoid Arthritis Outcome Study Group. Patients randomised to either an aggressive treatment or symptomatic treatment arm (both arms employing conventional disease modifying drugs) showed progressive deterioration of HAQ over a three year follow up [1]. These patients had a mean disease duration of 12.5 years, had failed on a mean of 1.4 previous DMARDs, and had a gradual HAQ deterioration of 0.15 over the three year follow-up [1]. This is important data on the response to conventional DMARDs in UK clinical practice, albeit in patients not exposed to anti-TNF at the time of follow-up.
    b. An important report from the BeSt study was discussed by the clinical specialists in the Appraisal Committee meeting, in which patients failing on methotrexate (up to 25mg) were highly unlikely to respond to any other disease modifying drug, either if replaced in sequential DMARD monotherapy, or if added to methotrexate in a combination therapy [2]. All patients going onto anti-TNF must have had a trial of methotrexate according to NICE guidelines, and therefore returning to conventional DMARDs following the failure of a first anti-TNF is highly unlikely to be an effective strategy. The ACD fails to adequately reflect this.

2. The fact that the BSRBR data is on patients where only 58% received concomitant methotrexate was discussed at committee, but is not mentioned in the ACD [3]. This is important because a large amount of data has emerged supporting the increased efficacy of combinations of anti-TNF with methotrexate. Consequently current UK practice would be always to combine the two unless methotrexate is not tolerated. No account has been taken of this in the analyses.

3. There was considerable discussion at the Appraisal Committee about concerns over rituximab being the only available biological therapy following the failure of the first anti-TNF. In particular our concerns surrounded the efficacy of these drugs in seronegative disease. The DANCER trial showed no efficacy in seronegative disease compared with placebo [4]. In REFLEX, the efficacy of rituximab in seronegative disease was reduced in comparison with seropositive disease [5]. The European League Against Rheumatism guidelines on the use of Rituximab suggest that it should not be used in seronegative disease [6]. Current trials of rituximab and the humanised form of the drug ocrelizumab are only being conducted in patients with seropositive RA. In the BSRBR 28% of patients were seronegative for rheumatoid factor [7]. This suggests that a substantial proportion of patients who go onto rituximab following the failure of a first anti-TNF are unlikely to gain a satisfactory response. By contrast, rheumatoid factor status does not predict the response to a second anti-TNF [7].

   The ACD makes no mention of the considerable discussion that took place around this point, which is not acceptable.

ii). Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?

We feel that the committee has failed to take all of the evidence into account on three counts:

1. We strongly disagree with the concluding sentence in 4.3.9 on page 25 of the ACD, and feel for all the reasons stated above, and the evidence we presented at the Appraisal Committee, that the effect of conventional DMARDs would be substantially less than that achieved in the placebo arm of the abatacept trial. We mentioned at committee that there is a considerable placebo effect of participating in a trail, receiving regular care and attention and placebo injections. This would artificially elevate the benefits of the placebo arm in the abatacept trial. We feel that the overall evidence would support substantially less benefit from patients returning to conventional DMARDs following the failure of anti-TNF, and the ACD does not interpret the evidence appropriately.

2. The comments in 4.1.10 do not reflect the highly contentious nature of analysis performed by the Decision Support Unit in the paper entitled "The effectiveness of non-biological DMARDs after anti-TNF α inhibitor failure." In summary, this analysis was performed on patients that have not previously failed a biological therapy, looks at EULAR response criteria and not change in HAQ, and makes assumptions about the impacts of increasing age, and disease duration that go well beyond the robustness of the data. We feel that it is inappropriate for the ACD to state that this study shows only slight decrease in EULAR response, when it is our strong feeling (expressed at the Appraisal committee) that this conclusion requires too many steps of faith.

3. We have no recollection of the conclusions of the discussions on discounting that are mentioned in 4.3.7 on pages 23 and 24 of the ACD. We know of no evidence to suggest that different discount rates would alter the cost-effectiveness of the BSRBR analysis which used

DAS28 as opposed to HAQ. We continue to feel strongly that the over-reliance on the BRAM to the exclusion of other models is inappropriate. We re-iterate that HAQ scores mainly reflect joint damage in established RA [8-10] and the impact on disease activity of biologics is more relevant in this group of patients than impact on function.

iii). Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

For all the reasons stated above we do not feel that these provisional recommendations are sound, and therefore do not constitute a suitable basis for the preparation of guidance to the NHS.

iv). Are there equality issues that may need special consideration?

We believe there are two equality issues that need consideration:

- Patients elsewhere in the world, including near neighbours such as the republic of Ireland and France, have far greater access to a first and a second anti-TNF at a time when the EC is trying to harmonise aspects of healthcare across different member states.

- Patients who are very disabled with high disease activity are discriminated against by the BRAM for the reasons we have highlighted above.

References

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4. Emery P, Fleischmann R, Filipowicz-Sonowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIb double-blind, placebo-controlled, dose-ranging trial (DANCER). Arthritis Rheum 2006;54:1390-400.

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7. Hyrich K, Watson K, Silman A, et al. Predictors of response to anti-TNF α therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology 2006;45:1558-65.
8. Aletaha D, Strand V, Smolen JS, Ward MM. Treatment-related improvement in physical function varies with duration of rheumatoid arthritis: a pooled analysis of clinical trial results. Ann Rheum Dis 2008;67:238-43.
9. Scott DL, Pugner K, Kaarela K et al. The links between jopint damage and disability in rheumatoid arthritis. Rheumatology 2000;39:122-32.
10. Scott DL, Smith C, Kingsley G. Joint damage and disability in rheumatoid arthritis: an updated systematic review. Clin Exp Rheumatol 2003;21(5 suppl 31):S20-7.

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19 May 2008

Dear Dr Longson,

Appraisal consultation document for adalimumab, etanercept and infliximab for rheumatoid arthritis

Please accept this letter as notification of Arthritis Care's support for the joint submission made by the Arthritis and Musculoskeletal Alliance (ARMA), Arthritis Care, The British Society for Rheumatology, the National Rheumatoid Arthritis Society and the Royal College of Nursing Rheumatology Forum in response to the ACD on the sequential use of adalimumab, etanercept and infliximab for rheumatoid arthritis.

Yours sincerely,

Dr Carole Longson,
Director, Centre for Health Technology Evaluation
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MidCity Place
71 High Holborn
London WC1V 6NA

19 May 2008

Dear Dr Longson

Re: ARMA Response to Sequential Use of Anti-TNF ACD

I am writing on behalf of The British Society for Rheumatology (BSR) to endorse the joint submission submitted by the Arthritis and Muscloskeletal Alliance (ARMA), Arthritis Care, The British Society for Rheumatology, the National Rheumatoid Arthritis Society and the Royal College of Nursing Rheumatology Forum.

We have worked closely with ARMA on this submission and fully support it.

Yours sincerely

[redacted]

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19 May 2008

Dear Natalie

Re: ARMA Response to Sequential Use of Anti-TNF ACD

I am writing on behalf of The National Rheumatoid Arthritis Society (NRAS) to endorse the joint submission submitted by the Arthritis and Muscloskeletal Alliance (ARMA), Arthritis Care, The British Society for Rheumatology, the National Rheumatoid Arthritis Society and the Royal College of Nursing Rheumatology Forum.

We have worked closely with ARMA on this submission and fully support it.

Yours sincerely

[redacted]

RCN Rheumatology Forum

19TH May, 2008

Dear Sirs,

The RCN Rheumatology Forum strongly supports the Arthritis and Musculoskeletal Alliance submission to NICE in relation to the ACD on sequential use of anti-TNFa therapies for Rheumatoid Arthritis.

The RCN will also be submitting a response to the above document.

Yours sincerely,

[redacted]