BSR
The British Society for Rheumatology

11 September 2015

Dear

Re: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed

The BSR is grateful for the opportunity to review the Final Appraisal Determination (FAD) for the above appraisal. We have liaised with our experts and wish to appeal the FAD. We wish to appeal on Ground 1a): that NICE has failed to act fairly, and also on Ground 2: that the recommendation is unreasonable in the light of the evidence submitted to NICE.

Background

This has been a protracted appraisal. Following the first appraisal meeting on the 15th October 2013, our experts challenged the methodology described in the assessment report in finding all ICERs to be above the threshold normally allowed by NICE for recommending a technology. Further analysis was undertaken by the DSU and amended just prior to the second appraisal committee meeting on the 21st May 2015. The BSR submitted expert opinion for both of these meetings but there was no mechanism to give written comments on the late amendment. Following the publication of the ACD, we submitted further expert opinion prior to the third meeting on the 22nd July 2015. We then had the first opportunity to provide written comment on the late amendment that indicated that the ICERs were lower for patients with the worst prognosis; in relation to moderate disease, the ICERs were £28,500 for those patients with the worst prognosis.

We welcome the committee's decision in relation to treatment of severe active rheumatoid arthritis. Although the criteria for treatment is tighter than current NICE guidance, we had recommended this change to the guidance, that patients needed to fail combination therapy rather than just two DMARDs, as we wanted to bring this in line with current clinical

guidelines and to support cost effective treatment. However we wish to appeal against the decision not to recommend treatment for patients with moderately active disease who have the worst prognosis.

There is a subset of patients with moderately active disease who fail to respond to combination therapy and have a poor prognosis. These patients will receive biologic DMARDs in most European countries[7]. In our submission following the ACD we gave one example of a study of 194 patients with RA who were treated with dose escalation of conventional DMARDs with a step up combination protocol[6]. The authors found persistent moderate elevation of DAS-28 was associated with important functional deterioration in 10-21% of early RA patients and a greater proportion of those with persistently moderate disease activity deteriorated than did those with persistently high disease activity.

In order to relate this to the ERAS cohort of patients used by the DSU, we commissioned an independent analysis of the ERAS database and informed the committee of the results in our submission following the ACD. In the whole ERAS database (1465 patients) there were 602 patients with a high HAQ progression defined as $\geq$0.06 p.a. This may be an overestimate because of a number of patients with low data points who had HAQ progression rates as high as 1.5 or 2 that may have biased the analysis. Nevertheless we analysed the data to determine the number of moderate patients who had rapid HAQ progression. There were 120 patients treated with methotrexate who *always* had a DAS score between 3.2 and 5.1; there was only a modest rise in the average HAQ of 0.017 p.a. in this group. However, even in this cohort 39 patients (32.8%) had an average HAQ progression of $\geq$0.06 p.a. We also evaluated the cohort of patients with a *mean* DAS score between 3.2 and 5.1 - a total of 868 patients. There were 319 patients in this group who had rapid HAQ progression of $\geq$0.06 p.a. (36.8% of those with a mean DAS of 3.2 to 5.1 and 53% of all patients in the whole ERAS database with rapid HAQ progression). These data are in keeping with published evidence that the majority of damage occurs in patients with moderate disease.

We explained in our written response how rheumatologists are able to identify patients who have a poor prognosis with progressive disease. In those defined as moderate with a DAS of 3.2 to 5.1, patients, we recommended very strict criteria for treatment with a biologic DMARD: only patients who had a positive ACPA (CCP) *and* radiographic erosions *and* raised

inflammatory markers. These are standard criteria used in clinical practice and we gave the committee some appropriate references [8-15].

Appeal Points

We wish to appeal on two Ground 1a points and one Ground 2 point.

Ground 1a) 1

NICE failed to act fairly by not giving the BSR an opportunity to make written representation regarding new important information in the assessment report prior to the second appraisal committee.

In the Guide to the Processes of Technology Appraisal 2014, it states at 3.7.3 that the committee papers consist of *"comments from consultees and commentators on the assessment report".* The BSR were unable to make written comments on the updated information in the assessment report prior to the appraisal meeting leading to the ACD.

The BSR made a written submission to the appraisal committee prior to the meeting on the 21st May 2015. This submission recommended the committee support treatment for patients with both severe and moderate disease. We argued that the committee would need to accept the discount rates used in the previous MTA. However, shortly before the meeting on the 21st May, NICE circulated a revised evaluation of the ICERs that had been produced by the DSU having located errors in the health economic analysis. This found ICERs that were within the £20,000 to £30,000 threshold for patients who could be identified with the worst prognosis *in both the severe and moderate groups*.

At the appraisal committee meeting, we argued that these new data supported the economic argument for treatment in both severe and moderately active rheumatoid arthritis. However, prior to the publication of the ACD we were denied the opportunity of providing a written submission that could explain how these groups could be defined. We made a written submission following the ACD. In view of this submission, our experts were invited to the third appraisal committee. Our proposals for treatment of moderate disease with the worst prognosis based on the new ICERs were dismissed in the FAD.

We have therefore been denied the opportunity to address the arguments in the FAD in response to our written submission. Had we been given the opportunity to have made a written submission regarding the new ICERs prior to the ACD, we would have been able to address the committee's argument. For example in the FAD (4.111) it states *'It was not persuaded that the alternative treatment criteria proposed could be currently used in decision-making'*. In reality, all rheumatologists use these criteria in decision making on a daily basis. The BSR does not have the opportunity to address these misconceptions by the committee. (Others are quoted in our Ground 2 point). This was therefore procedurally unfair.

Ground 1a) 2

It was procedurally unfair for the committee to reach a decision when it was apparent that not all members had read the relevant material.

In the Guide to the Methods of Technology Appraisal 2013 it states in 6.2.5..... *"This requires the Appraisal Committee to consider all of the evidence presented to it, including RCTs, observational studies and any qualitative evidence related to the experiences of patients, carers and clinical specialists who have used the technology being appraised or are familiar with the relevant condition"*. It was admitted at the appraisal committee meeting that this did not occur.

There was a short time scale to provide written response to the new information following the ACD. However, it is clear that this was an inadequate time period from responses at the committee. The Vice Chairman, , criticised our submission and stated that although he *'hadn't read the scientific papers (we referenced [1-19]), he had the read the titles'* and proposed that we were presenting a hypothesis rather than a factual response. One member complained that expanding the number of patients treated would increase the NHS budget, but other than Professor Milne the other committee members appeared to be sympathetic to the arguments we made. There was concern expressed from at least two committee members that the proposals were too rigorous and may deny some patients treatment. The fact that all the committee had not read the relevant material before the

meeting, suggests that they were not fully informed and this could potentially affect the outcome.

Ground 2

It is unreasonable to conclude that treatment for moderately active rheumatoid arthritis is not cost effective when the ICERs were in the range accepted by NICE.

In the Guide to the Methods of Technology Appraisal 2103 it states in 6.2.15..... *"the Committee will want to ensure that their judgements regarding the cost-effective use of NHS resources are consistently applied between appraisals".* However, despite the ICER for patients with moderate disease who have the worst prognosis being below £30,000, the committee did not approve treatment for these patients.

The ICERs presented by the pharmaceutical companies for treatment of moderate disease ranged from £18,721 to £26,952. The ERG evaluated the ICER of the moderate group with the worst prognosis to be £28,500 reducing to £20,462 for infliximab biosimilar. These ICERS are therefore within the threshold established by NICE to recommend treatment.

In response to the ACD, we had the first opportunity to inform the committee in written response how the patients with the worst prognosis are defined in clinical practice. There is a wealth of data to support the BSR's proposal to the committee regarding the criteria that could be used to limit biologic DMARDs in moderate patients to those with the worst prognosis. At the committee we explained these criteria in detail and how they are used in decision making in standard clinical practice. We gave several relevant references in our written response. For example in a study of 238 patients who were followed for 10 years[13] the authors concluded that *"Anti-CCP, IgM RF, ESR and female gender were independent predictors of radiographic progression and could be combined into an algorithm for better prediction. Patients with high levels of anti-CCP were especially prone to radiographic progression, indicating that the anti-CCP level may add prognostic information".* In response to questions whether we thought our criteria were too strict, we explained that there would be some patients who would progress that would not fulfil these criteria but the criteria would define those with the lowest ICER described by the Assessment Group.

We would wish to respond to some statements in the FAD to emphasise the unreasonable (negative) recommendation for patients with moderate disease.

4.94:

"The Committee supported the concept of identifying people likely to have rapid disease progression in order to target treatment with biological DMARDs. However, it noted that some of the criteria proposed are already used in rheumatoid arthritis diagnosis (for example, ACPA positivity) and that clinical experts suggested that, taken together, the measures would identify approximately one third to one half of patients with moderate active disease."

- This comment clearly indicates that the committee misunderstood the concept. Patients with rheumatoid arthritis who are not ACPA positive usually have less severe disease. Approximately one third of patients with moderate disease may have the worst progression and most would be defined by these criteria.

"The Committee was not persuaded of the sensitivity of the measures for identifying people with the fastest disease progression. The Committee also noted that, although individually validated, the measures were not necessarily independent of each other,"

- This is factually incorrect. We referenced the fact that they are independent factors[13].

"and different thresholds for presence or absence can be applied. It also noted that the effect of these different thresholds on speed of progression, when combined with thresholds applied for the other measures, was unclear."

- There aren't different thresholds. The thresholds are specific: positive or negative ACPA, erosions or no erosions, raised or normal inflammatory markers.

"It also noted that no economic modelling had been provided for this group,"

- This is incorrect. Those with the worst prognosis have an ICER of £28,500.

"and that it had not been provided with any clinical evidence to support the assumption that disease with these characteristics would respond well to biological DMARDs."

- We have not been given the opportunity. Most clinical trials have included patients with moderate disease with these criteria and these could be separated in an analysis.

4.109:

"The Committee agreed that the biological DMARDs should be considered an innovative class of drugs. It also noted the comments from patient experts that biological DMARDs provide extensive benefits for people with rheumatoid arthritis and their families, in terms of both physical and mental health. It understood that the physical health benefits associated with biological DMARDs may encompass improvements in pain and cardiovascular health and well as benefits to the musculoskeletal system. On balance, based on the range of the most plausible ICERs, the Committee concluded that biological DMARDs in combination with methotrexate were a cost-effective use of NHS resources for people with severe active rheumatoid arthritis previously treated with methotrexate."

- We consider it is unreasonable not to consider the same arguments for those with moderate disease.

We have presented the evidence that many of those patients defined as moderate do not have benign disease. Biological DMARDS provide the same extensive benefits for patients with moderate disease and yet despite the ICERs being within the threshold, and robust evidence to identify patients with the worst prognosis who would benefit the most, the committee did not support treatment for this group. We consider this is unreasonable in light of the evidence.

Yours sincerely,

BSR President **BSR nominated expert** **BSR nominated expert**

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