NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs have failed [ID537]

Decision of the Panel

Introduction

1. An appeal panel was convened on Thursday 26 November 2015 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs have failed [ID537].

2. The Appeal Panel consisted of –

   Dr Jonathan Fear – Chair
   Prof Marios Adamou – NHS Representative
   Mr Uday Bose – Industry Representative
   Mr Jonathan Tross – Non-Executive Director
   Dr Robert Thurstans – Lay Representative

3. None of the members of the Appeal Panel had any competing interest to declare.

   However, the Chair informed the hearing that Dr Frank McKenna, appearing for the British Rheumatoid Society was known to him and others on the Panel as Dr McKenna sits on the Institute's Appeal Panel. The Chair confirmed that there had been no correspondence between anyone on the Panel and Dr McKenna regarding the appeal. The Chair also noted that Prof Emery was known to him. The Chair did not consider there was any conflict of interest and there were no objections from the Appellants or the Appraisal Committee

4. The panel considered appeals submitted by –

   The British Society of Rheumatology (BSR) (professional group)
   National Rheumatoid Arthritis Society (NRAS) (patient group)

5. BSR was represented by –

Dr Frank McKenna
Prof Paul Emery

Prof Emery explained to the hearing that he had been involved with various manufacturers of the appraised technologies as an advisor and with their clinical trials.

6. NRAS was represented by-

Mrs Ailsa Bosworth
Prof Peter Taylor

Prof Taylor explained to the hearing that he had been involved with various manufacturers of the appraised technologies as an advisor and with their clinical trials.

7. All the above declared no conflicts of interest-

Dr McKenna reiterated that he was a member of the Institute's Appeal Panel and therefore knew members of the Panel. Dr McKenna confirmed that he had had no communication with anyone on the Panel regarding the appeal.

8. In addition the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel -

Prof Andrew Stevens – Appraisal Committee Chair
Prof Matthew Stevenson
Mrs Zoe Garrett
Ms Boglarka Mikundina
Dr Frances Sutcliffe
Dr Meindert Boysen

9. All the above declared no conflicts of interest

10. The Institute's legal adviser – Ms Eleanor Tunnicliffe of DAC Beachcroft LLP – was also present

11. Under the Institute's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

12. There are two grounds under which an appeal can be lodged:

Ground One: In making the assessment that preceded the recommendation, NICE has

a) **Failed to act fairly**
b) **Exceeded its powers.**

Ground Two: The recommendation is unreasonable in the light of the evidence submitted to NICE.

13. Andy McKeon, a non-executive Director of the Institute had confirmed that:

- BRS had potentially valid grounds of appeal as follows: 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.
- NRAS had potentially valid grounds of appeal as follows: 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.

(Ordinarily the Dr Helliwell in her role as vice-chair of the Institute would have considered the validity of the appeal points but Dr Helliwell considered she had a potential conflict of interest.)

Merck Sharp & Dohme had a potentially valid appeal point against the FAD but they withdrew their appeal prior to the hearing.

14. Treatment for rheumatoid arthritis usually includes non-steroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors, which reduce pain, fever, and joint swelling and inflammation, and disease-modifying anti-rheumatic drugs (DMARDs). DMARDs slow the disease process and reduce joint damage. More recently, a group of drugs has been developed including monoclonal antibodies and soluble receptors that modify the disease process by blocking key protein messenger molecules (such as cytokines) or cells (such as B-lymphocytes). Such drugs are referred to as biological DMARDs and the technology appraisal included 7 different biological medicines (in addition, for infliximab, there is an originator biological medicine and two biosimilar products available in the NHS).

For people with newly diagnosed rheumatoid arthritis, the NICE guideline CG79 on rheumatoid arthritis recommends a combination of conventional DMARDs (including methotrexate and at least 1 other conventional DMARD, plus short-term glucocorticoids) as first-line treatment, ideally beginning within 3 months of the onset of persistent symptoms. When combination therapies are not appropriate, conventional DMARD monotherapy is used.

15. The appraisal that is the subject of the current appeal provided advice to the NHS on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs have failed.

16. Before the Appeal Panel inquired into the detailed complaints the following made preliminary statement: Dr McKenna for BSR and Mrs Ailsa Bosworth for NRAS and Prof Stevenson behalf of the NICE Appraisal Committee.

Appeal Ground 1: In making the assessment that preceded the recommendation, NICE has

a) **Failed to act fairly**
b) **Exceeded its powers.**

17. There was no appeal under this ground.

Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.

Appeal Point Ground 2.1:

BSR – 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.

And

NRAS – 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 as cost effective.

18. With the agreement of all parties these appeal points were considered together.

19. Dr Frank McKenna on behalf of the BSR made the argument that it is unreasonable to conclude that treatment for moderately active rheumatoid arthritis in those with risk factors indicating rapid progression of the disease is not cost effective. Dr McKenna recommended that the Institute use standard prognostic factors as markers of rapid disease progression in addition to increased ACPA (anti-citrullinated protein antibodies). Dr McKenna explained that ERAS data was used to determine the number of patients with moderate disease who had rapid progression, using Health Assessment Questionnaire (HAQ) scores. About a third of patients were identified as having rapid disease progression. For this group the ICER

was less than £30,000. This was within the range acceptable by NICE.

20. Dr McKenna, also submitted that the ICERS for severe and moderate disease were very similar and that it was unreasonable to recommend treatment for those with severe disease but not for those with moderate disease. The benefits of treatment accepted by the Appraisal Committee for patients with severe disease also applied to those with moderate disease. The reasons given for not accepting that treatment was cost effective in the moderate group were factually incorrect and therefore unreasonable.

21. Mrs Ailsa Bosworth for NRAS emphasised the impact of moderate disease in people's lives.

22. Prof Andrew Stevens from the Appraisal Committee recognised Rheumatoid Arthritis (RA) as an important disease and also that antiTNFs used for its treatment are effective but also very expensive drugs. He reiterated that the ICERs for severe RA are £41,600 and moderate £51,100 and that the numbers quoted by the BSR referred to an extreme scenario that brought the ICER to £28,500 for some with moderate disease.

23. Prof Stevens explained that the Appraisal Committee noted that the Assessment Group had done an analysis using the rates of HAQ progression for those people whose disease was progressing fastest, and that this, on the basis of an assumption that such a group could be identified, reduced the base-case ICERs for the severe active population from £41,600 to £25,300 per QALY gained and from £51,100 to £28,500 per QALY gained for the moderate active population.

24. Prof Stevens elaborated that this analysis (based on HAQ scores) was retrospective – it was not based on pre-identifiable patient characteristics used to inform a decision about whether or not treatment should be given. The central question for the Appraisal Committee was whether alternative criteria for rapid progression could be identified, which could be used to inform treatment decisions.

25. The Committee was first presented with a suggestion of what these criteria might be at the ACD stage. It was suggested that this group could be identified based on persistent synovitis and failure of the disease to respond to combination therapy with conventional DMARDs plus:
    - persistent elevation of inflammatory markers
    - presence of erosions on X-ray and
    - positive for ACPA

    are strong predictors of rapid progressive disease.

26. The Committee carefully considered the suggestion. About half of the time at the final Committee meeting was devoted to this topic. Unfortunately, the proposal had not been developed to the extent that it could be

included in any economic modelling. It was not clear how the factors interacted with one another or what thresholds should be used for each of them. It fell far short of what was needed to identify patients with rapid progression. Moreover, the papers cited by BSR in support of their suggestion did not consistently identify the same predictors of progression.

27. Crucially, none of the factors listed were directly linked with the work done by the Institute's Decision Support Unit (DSU) to arrive at the £28,500 ICER for those with moderate disease with rapid progression. That analysis relied on favourable assumptions regarding patients about whom little was known, in particular that patients dropping out of the study would go on to have had the worst possible trajectory. Prof Stevens reflected that it would have been helpful if the FAD had explained that if the opposite assumption is made (a benign trajectory for all drop outs) the ICER would be in the region of £200,000.

28. Prof Stevens went on to explain that the factors identify approximately a third of patients in the moderate group. Clinical experts had informed the Committee that approximately a third to a half of patients with moderate disease experience rapid progression.

29. Given the most plausible ICER for the moderate group was £51,100, the Committee was unpersuaded that for a proportion as large as a half to a third of these patients the ICER was £28,500. That would mean that for a large number of the remaining patients the ICER was substantially higher than £51,100; such a spread of ICERs appeared not to reflect the clinical reality. Rather, the Committee considered that the £28,500 ICER was an optimistic one and the far end of the spectrum of possible ICERs and likely to apply to only 1-2% of patients.

30. The conceivable cost effectiveness range meant that even if it was possible to predict which patients with moderate disease would experience fast progression, it was still unlikely that treatment would be cost effective because the ICER for the moderate population (£51,100) was not a low enough starting point.

31. The Committee made recommendations for further research into factors that can predict the likelihood of rapid progression of disease.

32. Dr McKenna was concerned that the Appraisal Committee had taken into account the affordability to the NHS of a positive recommendation for those with moderate disease. This was not within the Institute's remit – the decision for the Committee was simply whether the interventions appraised were cost effective.

33. Dr McKenna went on to argue that the £28,500 ICER was not "the tail" but was applicable to all patients with moderate disease with significant progression. This was about a third of patients with moderate disease. He also raised concerns about the time available to consultees to

comment before the May Committee meeting.

34. Prof Emery submitted that the benefits to patients with moderate disease are greater than those with severe disease. It was preferable to treat early and then lower the dosage. Also, it was the level of inflammation that should be treated and not the pain and division of patients into moderate and severe groups using the DAS score did not achieve this.

35. Mrs Bosworth underlined the importance of treating inflammation before joints became damaged, in order to avoid surgery. Mrs Bosworth also emphasised the impact of moderate disease on patients – in one case a patient with moderate disease was out of work for 11 years spanning their mid-30s.

36. Prof Taylor noted that clinical guidelines from the US and the EULAR (the European League against Rheumatism) use the parameters for treatment suggested to the Appraisal Committee. He considered that the parameters indicating rapid progression in the papers cited to the Appraisal Committee were consistent. Prof Taylor referred to the Syvesen study, which used an algorithm to predict progression. He confirmed that at the end of the longitudinal study there were approximately 125 patients due to drop out rates. The trial was therefore not large but its findings could be validated in a further study.

37. Prof Stevens confirmed that the Appraisal Committee recommendations as made in the FAD did not take into account the prevalence of RA or the cost to the NHS by taking account of the number of patients who would qualify for treatment, but the ICERs discussed in the FAD did take into account the requirement in the methods guidance to be clear about uncertainty where costs were potentially high.

Conclusion and effect of the Appeal Panel's decision

38. The Appeal Panel concluded as follows.

39. The Appeal Panel was persuaded that the appropriate starting point for considering cost effectiveness in the moderate population was the ICER of £51,100. It considered this to be materially greater than the ICER for the severe population of £41,600. The Committee therefore did not act unreasonably when it concluded that treatment should be recommended for patients with severe disease and not those with moderate disease.

40. The Appeal Panel was further persuaded that the ICER of £28,500 for those with fast progression was at the extreme lower end of the spectrum of ICERs for those with moderate disease and rapid progression. It was satisfied by the Committee's explanation that it was not plausible for this level of ICER to apply to a half to a third of all moderate patients – the proportion of moderate patients the clinical experts considered would

experience rapid progression – given the ICER £51,100 for the total moderate population. The Appeal Panel was mindful of the statement in paragraph 5.10.6 of the Methods Guide that:

"The possibility of differences emerging by chance, particularly when multiple subgroups are reported, is high and should be taken into account. Pre-specification of a particular sub-group in the study or review protocol, with a clear rationale for anticipating a difference in efficacy and a prediction of the direction of the effect, will increase the credibility of a subgroup analysis."

It also noted that the £28,500 ICER was based on favourable assumptions being made about drop-outs and that if the converse assumptions are adopted then the ICER rises to approximately £200,000. The Appraisal Committee's consideration of the ICERs had been reasonable.

41. The Appeal Panel was satisfied that the Appraisal Committee's conclusion that it did not have a detailed enough proposal before it to use the suggested criteria to identify moderate patients likely to have rapid disease progression was a reasonable one. The material presented to the Committee in response to the ACD had not been developed to the point where it could be introduced into the economic modelling.

42. The Appeal Panel considered that lack of agreement between the Appellants and the Appraisal Committee around the evidence base for the identification of patients with moderate disease and likely rapid progression is indicative of the fact that further work needs to be carried out in this field. It did not consider that the Appraisal Committee had acted unreasonably. The Panel noted the complaint that consultees had not had enough time to comment. It also noted that BSR had attempted to raise this as a ground of appeal but that it had been held not to be a valid appeal ground at final scrutiny. The Panel therefore did not consider this point further.

43. The Appeal Panel considered whether it was unreasonable for the Appraisal Committee not to have done more to explore how a subgroup of moderate patients with rapid progression could be identified in practice. In particular, it considered whether the Appraisal Committee acted unreasonably by not asking for further work to be carried out regarding the development of an algorithm that could be included in the economic modelling.

44. The Appeal Panel concluded that given the base case ICER of £51,100 it was reasonable for the Appraisal Committee not to look into this further. It was reasonable for the Appraisal Committee to conclude that any father work was unlikely to identify a sub-group in which treatment was cost effective.

45. It also considered that given the substantial amount of work to be carried

out before an algorithm could be developed, the length of time the appraisal had already been underway and the need to produce guidance for the NHS, the Committee's approach was reasonable.

46. The Appeal Panel was satisfied that the Committee had based its recommendation on the ICERs set out in the FAD and not on overall costs to the NHS of a positive recommendation for patients with moderate disease.

47. The Appeal Panel dismissed all the grounds for appeal in this appraisal.

48. Although Appeal Panel has concluded that the Appraisal Committee acted reasonably, it considers that the FAD could be improved by explaining:
    - the favourable assumptions that lie behind the £28,500 ICER and setting out the approx. £200,000 ICER if converse assumptions are made (see in particular paragraph 4.111)
    - that the Committee did not find it plausible that the £28,500 ICER would apply to a third to a half of moderate patients (the proportion of moderate patients the clinical experts estimated would be identified by the suggested criteria) given the overall ICER of £51,100 for this group

    These are points that may be considered by the Guidance Executive.

49. There is no possibility of further appeal against this decision of the Appeal Panel. However, this decision and NICE’s decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of publishing the final guidance.