1. Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?

There is a paucity of good evidence for the anti-TNF agents in this context. There is uncontrolled evidence of the efficacy or RXB in combination with other DMARDs (eg Valleala et al. Scand J of Rheum 2009; 38: 323-7). This evidence could be used to support the use of RXB for patients who are intolerant of MTX.

2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations?

Emerging data from abstracts suggest that RXB is more effective when given at regular 6 month intervals. This would change the cost-analysis. Unfortunately this data is not yet available in peer reviewed journals as far as I am aware.

In addition, the SPC advises that RXB can be repeated at 4 months. The recommendation is therefore illogical to restrict it to 6 months if the patient has a good initial response but then flares. Current data suggest that response improves with subsequent infusions. It should therefore be possible to repeat the RXB at 4 months for the second infusion only. Subsequent infusions could then be repeated at 6 months or later.

3. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound?

I consider these recommendations to be unsound because they do not take into sufficient consideration the opinions of clinical specialists who are highly experienced in the management of patients with RA. It is accepted that there is an inadequate research basis on which to make this recommendation and because of this, greater weight should have been placed on best practice. In addition the recommendation is already out of date because it does not take into consideration Tocilizumab (TOC). If this recommendation is to go forward it should be with a predetermined short review date so as to be able to incorporate emerging data on the use of Rituximab in seropositive vs seronegative patients as well as the placing of TOC in the pathway.
4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland?

The pathways suggested in this appraisal would restrict treatment for patients in Scotland. At present it is possible to switch patients from one TNF treatment to another and all of us are very aware of the numbers of patients that benefit from the switch. Tocilizumab is also now available in Scotland and thus patients who fail one TNF are likely to be tried on either TOC or RXB. In view of the, albeit limited, suggestion that seronegative patients do not respond so well to RXB, it is likely that clinicians will try TOC instead.

5. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be.

The pathways would be changed for patients in Scotland. The current guidance in Scotland allows patients to receive either a second anti-TNF agent or RXB after initial failure of one TNF for whatever reason.

6. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case.

This guidance would represent a backward step for patients in Scotland and my opinion should not be adopted.

Consultant Rheumatologist

2. Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?

I would consider that the relevant evidence has been considered. It is noted that there are few RCTs and that the observational data do not allow conclusions to be reached with certainty

Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations?

I agree that the main conclusion, that Rituximab is a cost effective option following anti TNF failure is a reasonable interpretation of the clinical and cost effective evidence presented.

There is clearly great uncertainty regarding the magnitude of effect of a biologic agent against conventional DMARD and this uncertainty leads to the conclusion that other anti TNFs should not be used outwith a clinical trial environment. This is a fair conclusion, but a scenario based on conventional DMARD having efficacy equivalent to placebo could lead to ICERs that might be acceptable in a Scottish context. In Scottish practice the choice of “untried”
conventional DMARD is likely to be largely restricted to those agents considered to be of least utility and infrequently prescribed in modern practice

3. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound?

The provisional recommendations are sound as basis of guidance, though it needs to be recognised that not all technologies have been included in this appraisal

4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland?

The treatment pathways will differ in Scotland primarily due to the availability of Tocilizumab which has not been considered in this appraisal. It is currently accepted for use for DMARD failure and TNF failure, so could fit into the pathway before the first anti TNF or after. In reality, it is likely that it will be used primarily after both anti TNF and Rituximab (personal opinion). In addition the ORBIT study (starting 2010) will mean that some individuals will receive Rituximab before anti TNF, which would alter the sequence

5. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be.

At present, Scottish clinicians will often opt to use a second anti TNF agent on the grounds that the effectiveness of this approach is accepted. The implementation of this guidance would change this practice although it may be that the recent availability of Tocilizumab will already be reducing the extent to which “switching” between anti TNFs is practiced. The greater use of infusions (Rituximab and Tocilizumab) as opposed to subcutaneous agents that will likely result may be problematic for Rheumatology units in Scotland where there is often limited physical capacity and human resource

6. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case.

No, although responses to Q5 and Q6 will affect implementation

7. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment

It might be worth commenting on “stopping rules” which are discussed in the ACD. In general, stopping rules are adhered to in Scottish practice, though with varying degrees of rigour depending inter alia on whether viable options are available. Expert comment has indicated that there is little confidence in the use of “untried conventional DMARD” in this context. If an individual patient may only receive a maximum of 2 out of the range of biologic agents now licensed for use, it is likely that stopping rules will be less rigorously applied. Again the availability of a 3rd biologic in Scotland might mitigate this

Consultant Rheumatologist
3.

1. Do you consider that all the relevant evidence has been taken into account?
   
   Yes

2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence?

   I continue to have reservations about the BRAM model, particularly with respect to:

   • its’ failure to incorporate stopping rules into the model. Whilst there is some evidence from the BSRBR that some patients continue on treatment despite a failure to respond, these data are 1) limited by the nature of the BSRBR, which was not designed to collect disease activity or drug response data 2) of questionable relevance – the Committee questions whether the application of response criteria would be ‘reflective of clinical practice’ (p44). I would submit that the Committee should assess the cost effectiveness of therapy according to best practice. Experience of clinicians around the country shows that PCTs and HBs are increasingly auditing the use of anti-TNF carefully, and that drug continuation in the absence of response will be increasingly rare.

   • its over-optimistic assessment of the value of DMARD therapy in patients who have failed biologic therapy. The Committee recognise that the BRAM model probably over-estimates the magnitude of response to conventional DMARDs but it has not explored the issue of treatment longevity with conventional DMARDs. The assumptions about the duration of benefit from conventional DMARDs used by the BRAM model are not credible.

3. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?

   Not in my opinion, for the following reasons:

   • the Committee only considered anti-TNF therapy or abatacept as alternatives to rituximab. The conclusion that rituximab is the most cost-effective option for patients who fail anti-TNF therapy is probably correct, but a significant proportion of patients will fail to respond to rituximab. Leaving such patients without an option for further biologic therapy will generate significant unmet need and this will be associated with considerable personal hardship and suffering for the patients involved.

   • the Committee has given insufficient attention to that sub-group of patients which responds very well to therapy. The ICER for each of the drugs changes dramatically if the stopping rules change – so for instance, if patients were required to have a larger response in order to stay on treatment (for example by achieving a DAS28<3.2) it is probable that this would represent cost effective treatment. The evidence suggests that some patients do respond very well, for example, to abatacept following failure of an anti-TNF drug and the Committee should explore a risk-sharing scheme with the companies involved such that patients would be granted a trial of therapy free of charge, with the NHS only paying for subsequent therapy in patients with a good response.
4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland?

Yes, although tocilizumab is also approved for use in NHS Scotland in patients who fail anti-TNF therapy.

5. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland?

The total number of patients on anti-TNF therapy will grow less quickly if patients could not be switched from one drug to another, and the use of rituximab and tocilizumab is likely to grow correspondingly faster.

6. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales?

No

7. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment

No comment

Consultant Rheumatologist

4.

Comment to follow as soon as possible.

Consultant Rheumatologist

24 March 2010
Comments on the NICE ACD

The headings below are provided to guide your commenting. Please feel free to cover any other points which you think should be raised.

1. **Do you consider that all the relevant evidence has been taken into account?**
   
   Yes, although the available evidence is limited.

2. **Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence?**
   
   Yes

3. **Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?**

   The appropriate RCTs have been reviewed under the terms of reference set out by NICE.

4. **Are the patient pathways and treatment options described in the assessment applicable to NHSScotland?**

   There is a major difference in treatment pathways available in Scotland in that the SMC has passed tocilizumab (anti-IL 6 therapy) for use after one DMARD failure in RA.

5. **Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland?** Please see below.

6. **Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales?**

   Potentially, yes. As rheumatologists in Scotland are able to use tocilizumab early in the treatment pathway for RA, the patient population of TNF failures in Scotland is likely to represent a group of patients with more resistant disease, compared to the population of patients considered in the ACD i.e., patients in Scotland who fail anti-TNF therapy may have already failed anti-IL 6 therapy (and thus two biologic agents), compared to the NICE population, who will only have failed anti-TNF therapy. The role of a second anti-TNF drug in patients who have already failed two biologics has not, to the best of my knowledge, been subject to rigorous study.

7. **Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment.** No further comments.
Clinicians ACD Pro Forma

Expert Views on NICE Appraisal Consultation Document (ACD) Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

Provided by [Name Redacted] as an NHS QIS nominated clinical expert.