National Institute for Health and Clinical Excellence

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

Royal College of Nursing

Introduction

The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

Members of the RCN Rheumatology Nursing Forum reviewed this document on behalf of the RCN. We welcome this ACD which considers the very important issue of the use of further biologic agents following failure of traditional Disease Modifying Drug Therapies and one anti-Tumour Necrosis Factor alpha therapy. We fully recognise that a great deal of work has been undertaken to consider the complexities of the evidence for the appraisal of these technologies, however, we have some issues which we would wish to raise in responding to this ACD.

Appraisal Consultation Document – RCN Response

The RCN's response to the four questions on which comments were requested is set out below:

i) Has the relevant evidence been taken into account?

We recognise the challenges the Appraisal Committee has had to face in gaining evidence to undertake a robust and realistic evaluation of the true benefits (to the patient and the health economy) particularly when wider social costs cannot be considered. However, given this limitation, we feel the scope has considered the evidence available.

We note the Committee's comments in Paragraph 2.5 – With respect to missing data and the time frame taken for work disability to occur, there are no data for socio economic costs, including patients who reduce working hours / change work for sometimes lower paid employment. This can have a significant effect on patient's quality of life and their contribution to the wider economy.

Patient's quality of life is also largely affected by other aspects of rheumatoid arthritis such as pain, fatigue, and sleep disturbance which the report recognises in paragraph 4.3.15 as not being incorporated in the HAQ score. Failure to treat these aspects have the potential to affect a patient's function, and increase the individual's use of primary care services, and clinical nurse specialist facilities such as advice-lines and urgent appointments.

We would agree with the paragraph 4.3.10 that treatment effects for conventional DMARD's after failure of Anti TNF therapy would be limited, given that in order to meet the criteria for the use of TNF initially include failure to respond to conventional DMARD therapy.

ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?**

The Appraisal Committee themselves have highlighted mainly limitations to the cost effectiveness and interpretations made. We are concerned that despite attempts by all involved to input into the economic model that we still fail to capture the potential benefits to an individual rather than the group effect. Yet in reality we as clinicians are providing care to individuals who may actually benefit significantly and have a strong individual need for an effective treatment pathway. As we are making significant decisions based upon the group not the potential individual benefits of sequential use - we are significantly compromising some individuals' ability to benefit from subsequent treatments e.g. sequential use of a TNF inhibitor following failure of Rituximab. Particularly as yet it is difficult to identify the most appropriate pathway for an individual patient as research is not yet available to support the use of one or another Anti TNF therapy as a first option.

Where in the patient treatment pathway will Certolizumab pegol be placed?

In paragraph 4.1.6, the summary notes that 51% of patients only respond with an ACR 20 with Rituximab, whereas, paragraph 4.1.8 notes a 50% ACR 20 response to

Abatacept. There is no evidence to support the summarisation that the 50 % of patients who responded to Rituximab would have also responded to Abatacept or vice versa. Therefore 50% of patients who fail to respond to the first choice of anti TNF Therapy and Rituximab have no further treatment options available, despite there being the potential that they may respond to Abatacept given its different mode of action.

Treatment options for patients who are sero- negative remain limited (para 4.3.3).

Point: 4.3.20

The Appraisal Committee state in paragraph 4.3.20 that the current guidance on stopping treatment is not fully implemented in clinical practice, therefore, the response criterion had not been incorporated into the BRAM model. We are not clear what implication this has for the economic model. It does however highlight an issue that is likely to change as PCTs robustly monitor biologics use as their knowledge and understanding of the treatment and use of biologics improve and competencies of PCTs improve. It is hoped that this modelling did not compromise the overall cost effectiveness calculations to the detriment of the patient. This also means that the NHS resources are being more effectively used. In addition, if there are implications for the reality of delivering a range of treatment options to the patient, the challenge clinicians experience on the ground is that much of the time is taken up with paper work and negotiations with PCTs when patients fall outside the current criteria. It is likely that the greatest benefit would be that patients who have failed to gain sufficient benefit can be relatively easily identified.

We do not know whether the issues related exception reporting (requests for patients to be funded/ endorsed by the PCT for further treatment when they fall outside current NICE guidance recommendations) will be increased or reduced applying the proposed recommendations. The key issue is that the patient should continue to have their disease controlled and the pathway ensures that there are robust treatment criteria and clear rationale and monitoring of those failing to receive benefit progressing to the next effective treatment option. Anecdotally we suggest that it is likely that patients would prefer to progress to a further treatment at the cost of having ineffective treatment stopped. Was this considered in patient reports for this ACD?

If patients on biologics fail one treatment the same patient population will be moving onto a further treatment. The Committee in line with evidence suggest that 15% of

RA patients will have aggressive disease – this is likely to be the population who will continue to require biologic therapies with the current high disease activity score criteria. Is it the case that these cost savings in relation to stopping ineffective treatment are then transferred to benefit when patients transfers to an effective treatment?

Point: 4.2. 27

We understand that costs for hospitalisation and joint replacement were estimated using a cost per unit HAQ score but are unclear where the rationale/evidence for this approach has been validated?

We welcome the attempt to explore more fully the limitations of the HAQ score and considering evidence in relation to the EQ5D. A paper presented at ACR in 2009 (Neovius et al) shows that there are significant heterogeneity and that there are large subgroup differences that are likely to be important when using the EQ5D. They identify four distinct patient clusters first group consisting of patients with low pre-treatment utility who experienced major improvement, the second and third group consisting of patients with high or low pre-treatment utility changed little on average with a small fourth group with high utility as baseline deteriorated.

We note the comments by the Appraisal Committee that the results of using HAQ and EQ-5D scores were subject to considerable uncertainty. How did this impact upon the modelling decisions?

The National Audit Office Report (2009) reviewed the cost effectiveness of biologic therapies in the context of wider implications and costs to the NHS. They also produced an additional paper on health economics of their findings (NAO 2009). This evidence demonstrated that improved management including biologic therapies were cost effective if the analysis was considered over a five year period. Has the Appraisal Committee been aware of the modelling approach used by NAO and compared these with the current approach with BRAM?

We are unclear as to how important factors related to shortened life expectancy and increased poor outcomes related to cardiovascular disease have been considered in the model. We presume a short life expectancy is cost effective? Patients may not

die but face an additional health care burden such as cardiovascular disease or osteoporosis with its potential risk of fracture.

We would welcome clarity about the changing patterns of RA management as set out in the NICE RA management guidelines (2009) and how this approach would have been considered in the model. If as is hoped patients will be eligible for treatment with biologic therapies much earlier in their disease with less joint damage (however, they will as currently set out still have to achieve a high level of disease activity at a DAS ≥5.1).

Point: 4.3.13
Was the potential to avoid long term joint damage considered in the sense of previous models and future models considered?

It is also stated in this paragraph that a variety of analyses were undertaken and demonstrated that the ICERs were not very sensitive to changes in cost but more sensitive to changes in assumptions about natural history of disease (including DAS below 5.1?) and stopping treatment early (see Point 4.3.20). Would pressure to ensure treatment is stopped when ineffective be a good approach with a greater option for new therapies being offered?

Views on whether the resource impact and implications for the NHS are appropriate

See our response to paragraph 4.3.20 (above), and implications for PCTs and clinicians.

The additional workload for nurses will be as a result of spending more time with highly complex patients who have no effective treatment option, there will be psychological support particularly with respect to withdrawal of treatments, additional support for flare and poor disease control. The impact of this is likely to be an increase in the use of telephone advice line for support and liaison and an increase in the use of inpatient facilities for urgent access for inpatient beds (e.g. for intravenous methylprednisolone infusions). The long term consequences (>5 years) will be difficult to quantify depending upon future decisions but potentially a small group of patients will require high level nursing support related to symptom management, increased co-morbidities and surgery. For example, multiple joint replacements,

fusion of the neck to resolve instability due to erosion of odontoid peg, tissue viability issues such as managing patients requiring long term treatment for vasculitis and leg ulcers, pinch grafts and cardiovascular /osteoporosis management and associated fractures. This may be translated in the future into increased community nursing support and use of day care and or nursing home facilities.

The ongoing audit and data collection together with completion of specific reports to PCTs remain an important but additional workload for nurses.

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

We recognise the challenges in undertaking such complex modelling. However, we still perceive the evidence and the crafting within the models weighs rather heavily on the cost effectiveness components that are easily measurable and fails to balance these within the model of the wider healthcare and societal costs that we recognise remain a challenge with the NHS. Despite the challenges, we still feel it is important that these are given fair and detailed consideration before the final determination is made. We hope the modelling considerations in the NAO report and the focus on extending the model to a 5 year approach would be helpful.

iv) **Are there any equality related issues that need special consideration that are not covered in the ACD?**

The HAQ and the ACR 20, 50, 70 criteria are tools used to measure the group response and have not been used to evaluate within those groups the numbers of people who would have had an individual and significant benefit to treatment. This has true significance when social and wider health care perspectives fail to be adequately considered. Some patients will be affected by this ACD more than others but there are no specific issues otherwise to be considered.

We also consider that to only approve the use of a second TNF inhibitor in the context of research may be discriminatory. Although clinical trails endeavour to make stringent efforts to include persons from minority populations, the design of studies if they require good command of written English to complete questionnaires may exclude certain ethnic groups.

Access to research studies may also be dependant on the patient's locality, as research is often restricted to certain centres; therefore access to participate in research is not universal.

References:

Neovius, M., Gulfe II, A., Kristensen, Le, Nilsson, Jan-Åke, Karlsson, J., Geborek, P., et al; (2009) Biologic Therapy and Health-Related Quality of Life: Treatment Effect Heterogeneity in Patients with RA [abstract]. Arthritis Rheum 2009; 60 Supplement 10 :728
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