Comments from NACC on the Assessment Report for the MTA on infliximab and adalimumab for Crohn's Disease

Note:
Regrettably NACC did not receive the copy of the Report that was posted to it by the NICE Team in late January 2008 and only became aware of the invitation to comment on the 25th February 2008, two days before the deadline. NACC's comments are therefore preliminary and are focused more on the implications of the Report's conclusions for the guidance to be issued by NICE than on the technical work in the Report.

Use of infliximab for children who have Crohn's Disease

The authors of the Assessment Report conclude from their review of the evidence that they can make no assessment of the clinical or cost effectiveness of infliximab for Crohn's Disease in children. However, there is a gradually increasing use of infliximab in clinical practice for certain children where nutritional and other medical therapies have failed and where surgery is not considered to be the appropriate next treatment.

NACC is concerned that the guidance from NICE does not simply report that there is a lack of evidence of benefit and inadvertently create the opportunity for local NHS funding bodies to interpret that NICE has a negative view on this use and adopt a policy of not funding infliximab for any children.

The Guidance should

> *recognise that for some children who have severe Crohn's Disease that has not improved with nutritional or other medical therapy, infliximab offers a potentially valuable alternative treatment prior to or instead of surgery.*
>
> *require that the decision to use infliximab should only be made by a paediatric gastroenterologist (or paediatrician experienced in IBD linked with a paediatric gastroenterology unit) after careful discussion with the child and parents of the uncertainties and potential risks of anti-TNF treatment.*

NACC believes that, with the above limitations, NICE should give a positive recommendation for NHS funding to be available.

Consideration could be given to setting a relatively early review date in the hope that more evidence becomes available.

Use of infliximab for patients who have fistulas

This sub-group of patients is explicitly mentioned in the Scope and in the statement of the remit of the independent assessment at the beginning of the Report. However, in the text of the report patients with fistulas are sometimes mentioned and at others not. Importantly, the independent model and conclusions based upon it ignore the group of patients who have fistulas.

We presume the justification for this exclusion is the statement that in the company's model the figure for the QALY is substantially higher than the NICE threshold. In addition, in terms of clinical effectiveness, there are several references to a concern that the potential for infliximab to achieve closure of a fistula may not be a desirable outcome if this then creates an abscess.

The report refers to the development of the PDAI (Perianal Disease Activity Index) by clinicians who recognised that the CDAI (Crohn's Disease Activity Index) inadequately records these. However, it is unclear to us whether the specific factors assessed within the PDAI were taken into account in the development of the economic model to assess infliximab treatment of perianal fistulas due to Crohn's Disease.

From the patients' viewpoint, fistulas – particularly perianal fistulas – are among the most distressing consequences of Crohn's Disease and they have a major impact on patients' quality of life. There are very limited treatment possibilities and infliximab has been of real benefit to many patients even though its absolute effectiveness is not as great as we might wish. Even if the benefit is temporary there may be specific times or events in a patient's life when a temporary benefit may have huge value even if it is not long-lasting.

The concern about formation of abscesses expressed by the Report's authors has a basis in truth; sometimes infliximab may close a fistula but not heal it completely. However, the authors seem to imply that this possibility is a good reason for not recommending infliximab at all for this indication. Instead it should be understood that infliximab has a valuable place as part of an overall treatment strategy for fistulas in patients who have Crohn's Disease and that any sound clinical strategy will seek to avoid, monitor and respond to the formation of abscesses after closure.

NACC believes that NICE should recognise that infliximab has a value in the limited range of possibilities for the treatment of fistulas in Crohn's Disease. Reducing or closing a perianal fistula can greatly increase a patient's quality of life and we question whether this improvement is being sufficiently recognised in the economic modelling.

Anti-TNF treatment for induction of remission

NACC is pleased to see that the independent assessment supports the use of both anti-TNF therapies for induction of remission in both severe and moderate Crohn's Disease.

Episodic and maintenance use of anti-TNF treatment.

In their economic model, the authors of the Report have adopted what they acknowledge to be a 'simple' model contrasting induction treatment and maintenance treatment, and choosing not to address the question of episodic treatment (referred to as clinical discretion). Their justification for doing so is that episodic treatment is clinically indefinable, but we question whether this is a helpful approach. Given that episodic treatment is in effect one of the recommendations from the previous NICE Guidance on infliximab, which recommended that infliximab be administered again if a patient who had responded then relapsed, their decision seems surprising.

NACC may wish to make specific comments on the modelling which underpins the conclusions in the Assessment Report, particularly in relation to the modelling of maintenance treatment using anti-TNF therapy. Unfortunately, for the reasons given above, there has not been time for us to consider the detail of the modelling before writing this document.

On one issue we take a different view from the authors of the Report. They criticise one of the companies for excluding non-responders from their modelling of maintenance therapy. Whilst we accept that in the clinical trials and subsequent analysis it would have been very helpful to have full information about responders and non-responders (including late responders), in modelling the ongoing clinical application of anti-TNF treatment it seems sensible to exclude non-responders. If anti-TNF can be used for induction of remission, clinicians will presumably not consider for maintenance therapy any patient who failed to respond with induction therapy.

Sequential use of the two anti-TNF therapies.

Although the authors of the Report felt unable to make any recommendation because of lack of evidence, NACC believes both that it will be important for NICE to cover this issue in its recommendations in order to avoid different policies being adopted by NHS funding bodies and that NICE should recommend sequential use. As with paediatric use, this recommendation might have a relatively early review date. Evidence will quite quickly accumulate.

Recommendations concerning future clinical research

Many of these seem sensible and NACC hopes that they will guide future trials and research so that these important questions are answered.

Future developments

The authors note the increasing research into 'top down' use of anti-TNF therapy and whether this has significant long-term clinical and cost-effectiveness benefits. Although outside the current Scope, this factor should be taken into account in setting the review date.

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NACC
27th February 2008