NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Review Proposal Project (RPP) decision paper

Review of TA163; Infliximab for acute exacerbations of ulcerative colitis

Final recommendation post consultation
The guidance should move to the static list.
Rationale
In June 2017, the Institute published a surveillance report which recommended that TA163 should be updated in a subsequent update of CG166 (Ulcerative colitis: management). After further consideration in discussion with the developer, NICE Centre for Guidelines decided that an update of TA163 in response to new evidence would be unlikely to result in more than minor changes to the existing recommendations, and so the update has been deprioritised. Consequently, TA163 will not be updated and replaced in the update of CG166. Instead the recommendations will be incorporated. TA163 should move to the static list and the recommendations should remain extant.

1. Background

This guidance was issued in December 2008

At the Guidance Executive meeting of 27 June 2017 it was agreed that we would consult on the recommendations made in the GE proposal paper. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

The guidance should be updated in the ongoing update of CG166 (Ulcerative colitis: management).

3. Rationale for selecting this proposal

According to the NICE process guide section 6.20 technology appraisal can be updated within a clinical guideline if all of the following criteria are met:

- The technology falls within the scope of the guideline.
- There is no proposed change to an existing patient access scheme or flexible pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement.
- There is no new evidence that is likely to lead to significant changes in the clinical or cost effectiveness of a technology.

- The technology is well established and embedded in the NHS. The following may suggest that it is not well established or embedded:
    - spending on the technology for the indication that was the subject of the appraisal continues to rise,
    - there is evidence of unjustified variation across the country in access to the technology,
    - there is plausible and verifiable information to suggest that the availability of the technology is likely to be reduced if the funding direction were removed
    - the technology is excluded from the payment by results tariff.
- Stakeholder opinion, expressed in response to consultation on a review proposal for the technology appraisal, is broadly supportive of the proposal.

The technology appraisal guidance recommended infliximab "only in patients in whom ciclosporin is contraindicated or clinically inappropriate" (see Appendix A – Information from existing guidance). This was on the basis that the clinical and cost effectiveness of infliximab relative to ciclosporin was highly uncertain: there were no studies comparing the 2 drugs and the estimates of cost effectiveness were highly sensitive to the relative rates of colectomy. The new evidence identified from the literature searches now provides direct comparisons between the 2 drugs, however, these studies did not find significant differences between them, including in the rates of colectomy. Any benefits of infliximab over ciclosporin are likely to remain subject to uncertainty and this would be reflected in continued uncertainty about the cost effectiveness of infliximab versus ciclosporin. Consequently it could be argued that there is no new evidence that is likely to lead to significant changes in the clinical or cost effectiveness of a technology.

Infliximab has multiple indications and there are now biosimilar versions available, so it would be difficult to gauge the extent to which the technology is embedded in clinical practice based on spending alone. It is anticipated that consultation may clarify this point.

The use of infliximab potentially falls within the scope of the update of clinical guideline (CG) 166. The guideline will consider the broader context in which either infliximab or ciclosporin may be used. It is therefore recommended that a proposal for technology appraisal guidance TA163 to be reviewed in an update of CG166 is put forward for consultation.

4. Summary of consultee and commentator responses

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Respondent: Pfizer **Response to proposal:** Agree Please can you also consider the following evidence in the review: NIHR analysis of CONSTRUCT: https://www.ncbi.nlm.nih.gov/books/NBK368274/ It gives more information on the patient and professionals interviews which show a preference for infliximab over cyclosporin: Patients: “Participants express a liking for infliximab because of its positive outcome, relatively simple method of administration and lack of side effects.” HCPs: Professional interviews indicate a clear preference for infliximab among nurses. Most doctors are more equivocal and prepared to wait for evidence of effectiveness and safety before making up their minds. Some doctors are strongly in favour of infliximab, wishing to see it as the drug of choice in view of its ability to deal with the many complex symptoms this disease group displays; its ease of administration; fewer adverse side effects; greater familiarity; convenience; greater perceived effectiveness; and ease of handling. Ciclosporin is more cumbersome to administer and requires additional monitoring, which puts pressure on an already overstretched workforce. Professionals view nurse colleagues as more familiar with the administration of infliximab and note the fewer demands it puts on nurses’ time. Ciclosporin is more restrictive on patients’ movements, leaving them frustrated and in need of more intensive support from nurses who must be present to manage complications. Professionals question current NICE guidelines and government regulations around drug use and the restrictions that this places on their professional autonomy. Professionals want to gain a clearer understanding of how the drugs affect patients’ lives. Professionals complement the trial for shining a light on this area of study which they see as seriously under-researched.	**Comment from Technology Appraisals** Comment noted. The clinical guideline will no longer update the recommendations made in TA163. As a result the guidance will move to the static list of technology appraisals.

There's also a comment piece in the Lancet on the two studies: http://www.thelancet.com/pdfs/journals/langas/PIIS2468-1253(16)30016-4.pdf	

Respondent: The British Society of Gastroenterology **Response to proposal:** Agree • Of the main proposal to move the review of the use of Infliximab in acute severe ulcerative colitis (ASUC) from TA163 to the more general clinical guideline CG 166 (Ulcerative colitis (UC) management). This would seem to be a sensible move and one which the BSG can support. • I would agree that the intervening studies by Williams et al (CONSTRUCT)[1] and Laharie (GETAID CYSIF)[2] suggest that there is now good evidence not available at the time of TA163 review, comparing the use of ciclosporin and infliximab in the management of UC. Further these studies do appear to demonstrate similar efficacy and side effect profiles between the two drugs. • The review correctly states that since TA163 the cost of infliximab has substantially fallen due to the introduction of biosimilar infliximab. However I am concerned that the prices quoted are substantially higher than the day to day pricing of biosimilar infliximab of around £160 per 100mg vial and that all cost modelling should reflect this. • Increasingly IBD specialist units are using higher doses of infliximab in ASUC in patients with poor biochemical prognostic markers. These include enhanced induction regimes 0,1,2,6 week infliximab or the use of 10mg/kg. [3] It would be important for NICE to examine this evidence in particular reflecting new cost models in the CG166 review. • Given that we are now able to directly measure drug trough levels and that higher levels are associated with increased clinical response and mucosal healing physicians are able to tailor the dose of infliximab more accurately and to assess those patients who are primary non-responders versus those with high early	**Comment from Technology Appraisals** Comment noted. The clinical guideline will no longer update the recommendations made in TA163. As a result the guidance will move to the static list of technology appraisals.

clearance and corresponding low trough levels.[4,5] 1. Williams, J (2016a) Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. *Health technology assessment 1 (1):15-24* 2. Laharie, D (2012) Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. *Lancet* 380 (9857): 1909-15 3. Accelerated Infliximab rescue reduces early colectomy rate in acute severe ulcerative colitis. D Gibson et al. Clin Gastroenterol Hepatol. 2015;13:330-335. 4. Loss of Infliximab Into Faeces is Associated with Lack of Response to Therapy in Patient with Severe Ulcerative Colitis. Brandse JF et al. Gastroenterology 2015; 149:350-355. 5. Pharmacokinetic Features and Presence of Antidrug Antibodies associate with Response to Infliximab Induction Therapy in Patients With Moderate to Severe Ulcerative Colitis. JF Brandse et al. Clin Gastro Hep 2016;14:251-258.	

Respondent: Department of Health **Response to proposal:** No comment	**Comment from Technology Appraisals**

Respondent: Crohn's and Colitis UK **Response to proposal:** Agree We support the proposal to update this guidance in the ongoing update of CG166 (Ulcerative colitis: management). We would look forward to the opportunity to contributing further and to acting as a conduit for the experiences and input of people with IBD throughout the process of updating the guideline.	**Comment from Technology Appraisals** Comment noted. The clinical guideline will no longer update the recommendations made in TA163. As a result the guidance will move to the static list of technology appraisals.

Paper signed off by: Meindert Boysen, 15 February 2018

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