NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA163; Infliximab for acute exacerbations of ulcerative colitis

Original publication date:	December 2008
Review date	In 2011 the Institute decided to defer the decision to review TA163 until the completion of the GETAID CYSIF and CONSTRUCT trials. Both trials have now been completed.
Existing recommendations:	Optimised. To see the complete existing recommendations and the original remit for TA163, see Appendix A.

1. Proposal

The guidance should be updated in the ongoing update of CG166 (Ulcerative colitis: management). That we consult on this proposal.

2. Rationale

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.

3. Summary of new evidence and implications for review

Infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate. For patients who do not meet the criterion, infliximab is recommended only in clinical trials. Since 2008 the two studies (GETAID CYSIF and CONSTRUCT) were completed that compared infliximab and ciclosporin.

Laharie et al. 2017 reported results of open label, randomised controlled trial (GETAID CYSIF) that compared infliximab with ciclosporin. The trial recruited adults who had an acute severe flare of ulcerative colitis. In total 115 patients were randomly assigned to receive infliximab or ciclosporin. The results show that after a median follow-up of 5.4 years, colectomy-free survival rates (95% confidence interval [CI]) at 1 and 5 years were, respectively, 70.9% (59.2% to 82.6%) and 61.5% (48.7% to 74.2%) in patients who received ciclosporin and 69.1% (56.9% to 81.3%) and 65.1% (52.4% to 77.8%) in those who received infliximab (p=0.97) The authors concluded that long-term results further confirm a similar efficacy and good safety

profiles of ciclosporin and infliximab and do not favour one drug over the other in patients with acute severe ulcerative colitis refractory to intravenous steroids.

Williams et al. (2016a) reported the results of mixed methods, open-label, pragmatic randomised trial (CONSTRUCT) which recruited adults who had been admitted, unscheduled, with severe ulcerative colitis and could not respond to intravenous hydrocortisone within about 5 days. In total 270 patients were given either infliximab or ciclosporin. The results of the trial show that there was no significant difference between groups in quality-adjusted survival in the infliximab group area under the curve 564.0 (SD 241.9) versus 587.0 (SD 226.2) in the ciclosporin group; mean adjusted difference 7.9 ([95% CI -22.0 to 37.8]; p=0.603). Similarly there was no significant difference between groups in colectomy rates at 3 months (21% of patients in the infliximab group versus 25% of patients in the ciclosporin group), at 12 months (35% versus 45%) and overall (41% versus 48%).

Serious adverse events occurred in 16 patients receiving infliximab versus 17 patients receiving ciclosporin. The authors concluded that there was no significant difference between infliximab and ciclosporin.

Another paper by Williams et al (2016b) examined the cost effectiveness of infliximab compared with ciclosporin in addition to the clinical effectiveness that is described above. The cost effectiveness results showed that the total cost of infliximab was considerably higher than cost of ciclosporin. The study concluded that there was no significant difference between the two drugs in clinical effectiveness, colectomy rates, incidence of serious adverse reactions, or mortality, when measured 1-3 years post treatment. Patients will be followed up for 10 years to assess the long term outcomes of the both drugs. The results of interviews conducted as part of the study showed that the debilitating effect of ulcerative colitis; participants were more positive about infliximab than ciclosporin.

Has there been any change to the price of the technology(ies) since the guidance was published?
The list price of the originator infliximab product (Remicade) has not changed since the guidance TA163 was published £419.62 per 100 mg vial. Two biosimilar infliximab products (Remsima and Inflectra) became available in England at the list price of £377.66 per 100 mg vial. Infliximab products are available to the NHS at contract prices negotiated through the Commercial Medicines Unit. These prices are lower than the list prices but are commercial in confidence.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
Numerous changes to the summary of product characteristics however it did not result in any changes to the marketing authorisation conditions. Most of the updates are related to the drug safety and tolerability.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
In the original guidance TA163, the committee identified several uncertainties. Firstly, committee could not estimate the true clinical effectiveness of infliximab relative to a comparator drug – ciclosporin based on the evidence available at the time of the appraisal. However the committee was persuaded by the clinical specialists that the effectiveness of the two drugs was likely to be similar. Williams 2016 and Laheri 2017 concluded that infliximab is as effective as ciclosporin. Secondly, the committee was uncertain about the cost-effectiveness of infliximab because the model was sensitive to the colectomy rate and the company did not include adverse events and mortality in the cost effectiveness analyses. Williams et al (2016b) concluded that total costs of infliximab is higher than ciclosporin.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
Ulcerative colitis NICE guideline CG166 *See Appendix C for a list of related NICE guidance.*
Additional comments
N/A

The search strategy from the Evidence Review Group report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from December 2010 onwards (the date of the previous review proposal searches) were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix C for further details of ongoing and unpublished studies.

4. Equalities issues

No equalities issues were raised in the original guidance.

GE paper sign off: Meindert Boysen, 23 June 2017

Contributors to this paper:

Information Specialist: Tom Hudson

Technical Analyst: Irina Voicechovskaja

Associate Director: Janet Robertson

Project Manager: Samantha Shannon

Centre for Guidelines: Peter Shearn

Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of infliximab for ulcerative colitis.

6. Current guidance

1.1 Infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient.

1.2 In people who do not meet the criterion in 1.1, infliximab should only be used for the treatment of acute exacerbations of severely active ulcerative colitis in clinical trials.

7. Research recommendations from original guidance

"The Committee recommended that infliximab and ciclosporin should be directly compared, exploring the clinical effectiveness of the two therapies in the treatment of acute exacerbations of severely active ulcerative colitis.

The Committee noted that there are two ongoing studies relevant to this guidance:

- *A study comparing ciclosporin with infliximab in steroid-refractory severe attacks of ulcerative colitis (sponsored by the Group d'Etude Thérapeutique des Affections Inflammatoires Digestif [GETAID]).*

- *A study comparing the effectiveness of ciclosporin with infliximab in the management of acute ulcerative colitis refractory to intravenous corticosteroids (CONSTRUCT – comparison of infliximab and ciclosporin in steroid resistant ulcerative colitis; a trial), School of Medicine, Swansea University".*

8. Cost information from original guidance

"Infliximab (vial with powder for reconstitution) is available at a net price of £419.62 for a 100-mg vial (excluding VAT; 'British national formulary' [BNF] edition 55). The drug cost varies from patient to patient because the dose is adjusted to each patient's body weight. For example, for a person weighing 73 kg the cost per infusion (if no vial sharing is assumed) would be £1678.48, corresponding to four vials of 100 mg for a dose of 365 mg. Therefore, for a 'course' of infliximab, assuming three doses, the drug cost is £5035.44. Costs may vary in different settings because of negotiated procurement discounts" (NICE TA163, December 2008).

The cost of Remicade, the only formulation of infliximab available at the time of TA163, remains the same as given in the original TA. Since the publication of

Appendix A

TA163 biosimilar versions of infliximab have received marketing authorisations. Infliximab biosimilars are available at list prices from £377 per 100-mg (powder for concentrate for solution/ infusion; C+D data [online], accessed 3rd January 2017). All the products are available in the NHS at prices lower than list price.

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Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA or MTA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred (to a specified date)	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix A

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	**Yes**
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	No
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

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Appendix C – other relevant information

1. Relevant Institute work

Ulcerative colitis: management in adults, children and young people (2013) NICE guideline CG166

Vedolizumab for treating moderately to severely active ulcerative colitis (2015) NICE technology appraisal guidance 342

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (2015) NICE technology appraisal guidance 329

Ulcerative colitis: budesonide multimatrix (Cortiment) (2015) NICE evidence summary 58

Inflammatory bowel disease (2015) NICE quality standard 81

2. Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Tofacitinib (Pfizer)	Phase III for acute and maintenance treatment of moderate-severe ulcerative colitis.	Yes [redacted]
Ustekinumab (Janssen)	Phase III for moderate-to-severe active ulcerative colitis in adults	Yes. [redacted]
Alicaforsen (Atlantic Healthcare)	Phase III for distal ulcerative colitis - second-line after antibiotics have proven inappropriate or ineffective	Yes [redacted]
Infliximab biosimilars (various)	Two infliximab biosimilars have been launched in the UK. Others are in the pipeline.	n/a
Vedolizumab (Takeda)	Phase III as a subcutaneous maintenance treatment in people with moderately to	No

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	severely active ulcerative colitis	
Ozanimod (Receptos)	Phase II/III for moderate-to-severe active ulcerative colitis	No
Filgotinib (Gilead Sciences)	Phase III for ulcerative colitis	No
Kappaproct (InDex Pharmaceuticals)	Phase II for chronic active moderate to severe ulcerative colitis.	No
Phosphatidylcholine (Dr Falk)	Phase III for ASA refractory ulcerative colitis	No
Etrolizumab (Roche)	Phase III as induction/maintenance treatment in people with moderate-to-severe, active ulcerative colitis who are refractory to or intolerant of TNFinhibitors	No

3. Registered and unpublished trials

Trial name and registration number	**Details**
A Study to Evaluate the Effectiveness and Safety of Infliximab in Chinese Patients With Active Ulcerative Colitis NCT01551290; CR018769; REMICADEUCO3001	Infliximab vs. placebo n = 99 Completed October 2014

Appendix C

Trial name and registration number	Details
A Long Term Safety Study of Infliximab (Remicade) inUlcerative Colitis Patients NCT00207688; CR004801; C0168T62	Long-term (up to 5 year) observational follow-up of participants from active and placebo arms of previous infliximab studies. n = 505 Completed September 2015
A Randomized, Multicenter Open Label Study Comparing Early Administration of Azathioprine Plus Infliximab to Steroids Plus Azathioprine for Acute Severe Colitis NCT02425852; ACTIVE; GETAID 2015-02	n = 150 Estimated completion date: September 2017 (primary outcome); March 2018 (overall).

Appendix D – References

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

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*

Williams J (2016b) Comparison of infliximab and ciclosporin in steroid resistant ulcerative colitis: pragmatic randomised trial and economic evaluation (CONSTRUCT). *Health technology assessment* 20 (44): 1 – 320.