NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA140 infliximab for subacute manifestations of ulcerative colitis and TA163 infliximab for the treatment of acute exacerbations of ulcerative colitis.

TA 140 was issued in April 2008. The review date for this guidance is February 2011.
TA 163 was issued in December 2008. The review date for this guidance is December 2011.

Recommendation

- A decision to review TA163 should be deferred until the completion of the GETAID CYSIF and CONSTRUCT trials.
- A decision to review TA140 should be deferred until the completion of the single technology appraisal of adalimumab for the second-line treatment of moderate to severe ulcerative colitis (referred November 2010).
- That we consult on the proposal.

Consideration of options for recommendation:

Options	Comment
A review of the guidance should be planned into the appraisal work programme.	There is currently not enough new evidence to recommend a review. The relevant clinical trials have not yet reported.
The decision to review TA163 should be deferred until the completion of relevant trials.	**There are several ongoing clinical trials that are due to report in 2011 and 2012. The relevant trials include GETAID CYSIF study and CONSTRUCT and these compare infliximab with ciclosporin. This comparison was a recommendation for further research in TA163.**

Options	Comment
A review of TA140 should be combined with a review of a related technology and conducted at the scheduled time for the review of the related technology.	**An appraisal of adalimumab for the second-line treatment of moderate to severe ulcerative colitis has recently been referred. This is the same place in the treatment pathway as addressed in TA140. It is proposed that a decision to review infliximab is deferred until the outcome of this appraisal is known, so that, if appropriate it can be proposed that the appraisals are reviewed together.**
A review of the guidance should be combined with a new appraisal that has recently been referred to the Institute.	Adalimumab for the second-line treatment of moderate to severe ulcerative colitis has recently been referred. To provide timely guidance to the NHS on adalimumab it would not be appropriate to incorporate a review of the infliximab guidance with this referral.

Options	Comment
The guidance should be incorporated into an on-going clinical guideline.	A clinical guideline on the management of ulcerative colitis was referred in November 2010. It is not timely to incorporateTA163 within this clinical guideline because there are studies expected to be published with in the next 2-3 years that may cause the guidance to change. One of the studies will provide UK data on the clinical effectiveness of infliximab compared with ciclosporin and key economic/health-related quality of life data. The clinical guideline could **refer** to TA163 but should not incorporate the guidance as it is likely that it will change within the lifetime of the guideline. There is no new evidence to suggest that the guidance in TA140 will change. However, given that there is an ongoing appraisal of a related drug, adalimumab, for ulcerative colitis it is not appropriate to incorporate TA140 into the clinical guideline while the outcome of the related appraisal remains unknown. The clinical guideline could refer to the TA guidance but should not incorporate it.
A review of the guidance should be updated into an on-going clinical guideline.[1]	A remit for a guideline on the management of ulcerative colitis was referred in November 2010. See above. TA 163 and TA140 do not meet the criteria for updating within a clinical guideline – see appendix A.

[1] See Appendix A on page 4

Options	Comment
The guidance should be transferred to the 'static guidance list'.	This option is not appropriate as there are ongoing clinical trials relevant to the recommendations for further research in TA163. With the development of a clinical guideline for ulcerative colitis and the referral of adalimumab for the treatment of ulcerative colitis, there may be changes to the clinical management of ulcerative colitis which mean it would not currently be appropriate for TA140 to be placed on the static list.

Original remits

TA 140
To appraise the clinical and cost effectiveness of infliximab for moderately to severely active ulcerative colitis.

TA 163
Remit: To appraise the clinical and cost effectiveness of infliximab for ulcerative colitis.

Appraisal objective: To appraise the clinical and cost effectiveness of infliximab for the treatment of acute exacerbations of severely active ulcerative colitis that require hospitalisation.

Current guidance

TA140
This guidance relates only to the use of infliximab for subacute manifestations of moderately to severely active ulcerative colitis. The guidance does not cover the use of infliximab for acute manifestations of moderately to severely active ulcerative colitis.

1.1 Infliximab is not recommended for the treatment of subacute manifestations of moderately to severely active ulcerative colitis.

1.2 For the purposes of this guidance, a subacute manifestation of moderately to severely active ulcerative colitis is defined as disease that would normally be managed in an outpatient setting and that does not require hospitalisation or the consideration of urgent surgical intervention.

TA 163
This guidance relates only to the use of infliximab within its marketing authorisation, for the treatment of acute exacerbations of severely active ulcerative colitis. It relates to an induction course of three doses of infliximab.

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.

Relevant Institute work

Published

Percutaneous endoscopic colostomy. IPG161. Published: March 2006.

Leukapheresis for inflammatory bowel disease. IPG126. Published: June 2005.

In progress

Management of ulcerative colitis. Clinical Guideline. Referred: 30 November 2010. Remit: To produce a clinical guideline on the management of ulcerative colitis.

Colonoscopic surveillance for prevention of colorectal cancer in patients with ulcerative colitis, Crohn's disease and polyps. Short Clinical Guideline. Publication date: TBC (Pre-publication check completed November 2010).

Adalimumab for the second-line treatment of moderate to severe ulcerative colitis. Technology Appraisal. Referred: 21 September 2010.

In topic selection

[redacted]

Details of changes to the indications of the technology

Drug (manufacturer)	Details
Infliximab	No changes since April 2008.

(Merck Sharp & Dohme/Schering Plough)	[redacted]

Details of new products

Drug (manufacturer)	Details
Adalimumab	Adalimumab for the second-line treatment of moderate to severe ulcerative colitis has recently been referred. Referral date: September 2010 Expected licence date: [redacted]
Golimumab (Simponi), MSD	Phase III clinical trials for moderately to severely active ulcerative colitis.
Alicaforsen (Oligo-TCS), Atlantic Healthcare	Phase III clinical trials for ulcerative colitis.
Vedolizumab (MLN0002), Millennium Pharmaceuticals	Phase III clinical trials for moderate to severe ulcerative colitis. [redacted]

On-going trials

Trial name and contact	Details
Study Comparing Cyclosporine With Infliximab in Steroid-refractory Severe Attacks of Ulcerative Colitis (CYSIF) NCT00542152 Phase IV Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives (GETAID)	Status: Completed Enrolment: 110 Start date: June 2007 Completion date: June 2010 Purpose: To compare the efficacy of cyclosporine with infliximab in steroid-refractory attacks of ulcerative colitis.

Trial name and contact	Details
Comparison of infliximab and ciclosporin in Steroid Resistant Ulcerative Colitis: a Trial (CONSTRUCT) ISRCTN: 22663589 Phase III Swansea University School of Medicine	Status: Open Enrolment: 1400 Start date: September 2008 Completion date: August 2012 Expected publication on HTA website – late 2013 Purpose: The study comprises a cohort and a randomised controlled trial (RCT). The overall aim of the RCT is to compare the clinical and cost effectiveness of infliximab and ciclosporin for patients with steroid resistant UC. Patients will be followed up at intervals of 3, 6, 12 and 24 months after initial treatment and it is hoped all these patients will be followed for at least 10 years using routinely collected data.
Efficacy & Safety of Infliximab Monotherapy Vs Combination Therapy Vs AZA Monotherapy in Ulcerative Colitis (Part 1) Maintenance Vs Intermittent Therapy for Maintaining Remission (Part 2) (Study P04807AM3) NCT00537316 Phase III Schering-Plough	Status: Completed Enrolment: 600 Start date: February 2007 Completion date: February 2010 Purpose: Part 1 Comparison of the Efficacy and Safety of Infliximab, as Monotherapy or in Combination With Azathioprine, Versus Azathioprine Monotherapy in Moderate to Severe Active Ulcerative Colitis Part 2 Comparison of Maintenance Versus Intermittent Infliximab Treatment in Maintaining Remission: A Follow-Up of Efficacy and Safety.

Trial name and contact	Details
Conventional Step-Up Versus Infliximab Monotherapy in Patients With Ulcerative Colitis (Study P05553) (MUNIX) NCT00984568 Phase III Schering-Plough	Status: Recruiting Enrolment: 400 Start date: November 2009 Completion date: June 2012 Purpose: This study will be performed to directly compare the efficacy and safety of the classical "Step-Up" approach for treatment of moderate to severe active ulcerative colitis using prednisolone and 5-aminosalicylic acid (5-ASA) and oral azathioprine (AZA) with a more intensive and early "Top-Hold" approach with infliximab (5 mg/kg) continuously given every 8 weeks following induction at weeks 0, 2, and 6.
A Long Term Safety Study of Infliximab (Remicade) NCT00207688 Phase IV Centocor	Status: Ongoing, not recruiting Enrolment: 284 Start date: June 2004 Completion date: 5 years after the end of the primary study.
European Safety Registry in Ulcerative Colitis (Study P04808AM3) NCT00705484 Observational Schering-Plough	Status: Recruiting Estimated enrolment: 2000 Start date: June 2007 Completion date: December 2016 Purpose: a prospective, safety surveillance registry in subjects with moderate-to-severe active ulcerative colitis.

Proposal for updating the guidance

If the guidance is to be updated as an appraisal, it would be scheduled into the work programme accordingly.

New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline(R) In-Process and Embase. References from 2007 onwards were reviewed. The results of the literature search are discussed in the ‘Appraisals comment’ section below.

Implementation

No submission was received from Implementation.

Equality issues

No issues were described in the original guidance.

Appraisals comment

In Technology Appraisal (TA) number 163, infliximab was 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. Ciclosporin was a key comparator in this appraisal and infliximab was considered not to be cost effective for those patients for whom ciclosporin was a treatment option. There have been no changes to the marketing authorisation for infliximab and no new interventions or comparators have come to market since the original guidance was issued.

Two trials (the GETAID CYSIF study and the CONSTRUCT study) comparing infliximab to ciclosporin in severe acute ulcerative colitis were mentioned as ongoing in the recommendations for research in the original guidance for TA163 and are therefore relevant to the review. The GETAID CYSIF study was due to complete in June 2010 and to publish in February 2011 (ECCO conference). The CONSTRUCT study is not due to complete until August 2012 and not expected on the HTA website until late 2013. Importantly, the CONSTRUCT study, funded by the NIHR/NETSCC, is being conducted in the UK and collecting resource use and EQ-5D data.

In Technology Appraisal (TA) number 140, infliximab was not recommended as an option for the treatment of subacute manifestations of moderately to severely active ulcerative colitis. No clinical studies were identified in the searches that suggest that this recommendation would change if the appraisal were to be subject to review. The MUNIX trial is ongoing but the patients included are those not previously treated for ulcerative colitis and is therefore out with the current marketing authorisation for infliximab that specifies inadequate response to conventional therapy.

Adalimumab for the treatment of moderate to severe ulcerative colitis was referred to NICE as an STA in September 2010. To provide timely guidance for adalimumab to the NHS, it would not be appropriate to incorporate a review of the infliximab guidance with this referral. However, given that the two technologies are for use at the same point in the treatment pathway, it would be appropriate to consider once the outcome of the appraisal of adalimumab is known whether the technologies should be reviewed together.

The management of ulcerative colitis was referred to NICE as a clinical guideline in November 2010. It is not considered appropriate to update TA163 within this clinical guideline as at least one of the key trials is not due to report until at least August 2012 and to be available on the HTA website in late 2013. This would mean that, if the review were to be updated in the clinical guideline prior to December 2012, key data may be omitted. It is not considered appropriate to review or incorporate TA140 into the guideline as a review is not currently considered timely, but may become so once the outcome of that appraisal of adalimumab is known.

Implications for other guidance producing programmes

CCP have been asked to develop a joint clinical guideline and quality standard for the management of ulcerative colitis. The work is in the early stages of the scoping and the draft scope of the clinical guideline and quality standard for consultation will be confirmed at the scoping workshop scheduled on 26/05/11. Publication is scheduled for June 2013.

Key issues

There are two trials relevant to the review of TA163, one of which (CONSTRUCT) has been conducted in the UK. It is recommended that the decision to review TA163 should be deferred until the results of both studies are available.

No new evidence has been found in relation to TA140. The MUNIX study relates to previously-untreated ulcerative colitis, which is not covered by the current marketing authorisation. A single technology appraisal of a related drug (adalimumab) for the second-line treatment of ulcerative colitis is ongoing. Rather than move the appraisal to the static list and incorporate the recommendations in the clinical guideline, it would be appropriate to revisit the decision to review when the outcome of the adalimumab appraisal (including its recommendation in relation to review of the guidance) is known.

GE paper sign off: Jenniffer Alty, 17 03 2011

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APPENDIX A – Updating Technology Appraisals in Clinical Guidelines [redacted]

Typically, a TA is likely to be suitable for updating in the context of a clinical guideline if all the conditions below are met.

Condition	Met – YES/NO
i. The technology falls within the scope of a clinical guideline (or public health guidance)	Yes, a clinical guideline for the management of ulcerative colitis was referred in November 2010.
ii. 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	Yes, there was no patient access scheme proposed
iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment	No, for TA 163 there are ongoing clinical studies on infliximab in UC are expected to report in 2013. The outcome of these studies may result in a change to the guidance. For TA140 there is no new data that would change the guidance, but there is an ongoing appraisal of a related drug. It would be preferable to review TA140 when the outcome of that appraisal is known.

Condition	Met – YES/NO
iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include; • Spending on a treatment for the indication which was the subject of the appraisal continues to rise • There is evidence of unjustified variation across the country in access to a treatment • There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed • The treatment is excluded from the PbR tariff	No information available
v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.	To be informed by consultation