NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA329; Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy

Original publication date:	25 February 2015
Review date	February 2018
Existing recommendations:	All 3 products are recommended. See appendix A for the complete list of recommendations and the original remit for TA329

1. Proposal

The guidance should be transferred to the 'static guidance list'.

2. Rationale

Technology appraisal TA329 was a review of 2 technology appraisals TA140 (Infliximab for subacute manifestations of ulcerative colitis), TA262 (Adalimumab for the treatment of moderate to severe ulcerative colitis) and an appraisal of golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy.

Since the original guidance there has been no direct evidence from head-to-head trials of adalimumab, infliximab and golimumab. As such, there is no new clinical evidence that would change the recommendations of TA329. The companies have confirmed that no changes are anticipated in marketing authorisations or costs. However the price of infliximab varies depending on whether the reference version of infliximab or biosimilar versions are used. The availability of infliximab and adalimumab biosimilars will not change the recommendations; the recommendations specify that if more than 1 treatment is suitable, the least expensive should be chosen.

3. Summary of new evidence and implications for review

Infliximab, adalimumab and golimumab are recommended for treating moderately to severely active ulcerative colitis after the failure of conventional therapy. Since 2015 a phase 3b, multicentre, multi-country, open-label, uncontrolled study InspirAda (Travis 2017) has been completed. The study evaluated the quality of life and economic impact of adalimumab in 463 patients with ulcerative colitis. The results showed that adalimumab therapy in usual clinical practice is effective at improving and maintaining symptomatic control of the disease and at improving health related quality of life, which is in line with the evidence considered for TA329.

Confidential information has been removed. © NICE 2018. All rights reserved. Subject to Notice of rights.

Several studies on use and effectiveness of biosimilar products have been published. All studies show that biosimilar drugs have similar clinical effect as the reference drugs however switching to biosimilar drug requires further investigation.

The availability of biosimilars (infliximab and adalimumab) has cost implications. However, it is not anticipated that this is likely to impact the recommendations in TA327; the recommendations specify that if more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).

Has there been any change to the price of the technology(ies) since the guidance was published?
Since the appraisal, the new biosimilar for infliximab (Flixabi, Biogen Idec) received a marketing authorisation in 2016. Flixabi price for 100 mg powder is £377.00. Also the list price for other biosimilars became available. Inflectra (Hospira UK) and Remsima (Napp Pharmaceuticals) 100mg powder for concentrate for solution for infusion vials cost £377.66. The price for reference infliximab (Remicade, Merck Sharp & Dohme) has not changed: £419.62. Adalimumab (Humira, AbbVie) price for a pre-filled 40 mg pen or syringe, or a 40 mg/0.8 ml vial has not changed: £352.14. In 2017, 4 new biosimilars for adalimumab (Amgevita, Amgen Europe; Cyltezo, Boehringer Ingelheim International; Imraldi, Samsung Bioepis; Sylombic, Amgen Europe) received marketing authorisation. The list price for biosimilar drugs is not known. The price of golimumab (Simponi, Merck Sharp & Dohme) has not changed: £762.97 for a pre-filled 50 mg pen or syringe and £1525.94 for a 100 mg pre-filled pen. The complex patient access scheme has not changed. BNF was accessed for all drugs prices on 27 November 2017.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
No changes to the marketing authorisations have been made or proposed.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
The committee would have liked to consider further evidence on the outcomes for patients with ulcerative colitis who stop TNF-alpha-inhibitor therapy after achieving remission. The committee also identified that the network meta-analysis results did not allow it to establish the relative effectiveness of the TNF alpha inhibitors. None of the new studies address these issues.
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.

Confidential information has been removed. © NICE 2018. All rights reserved. Subject to Notice of rights.

Guidelines have confirmed that there is no overlap between the review of TA329 and the guideline update of CG166 as the guideline update is only looking at mild to moderate ulcerative colitis. TA329 looked at moderate to severe UC. Infliximab, adalimumab and golimumab do not have a marketing authorisation for mild-moderate disease and are not normally used in this population. *See Appendix C for a list of related NICE guidance.*
Additional comments
N/A

The search strategy from the original Assessment Report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2014 onwards 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 above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

During the development of TA329 a potential equality issue was identified; the recommendations could lead to patients with ulcerative colitis having elective or potentially emergency surgery if TNF alpha inhibitors cannot be offered, in particular:
- Young people who have not begun a family and whose fertility may be affected by the surgery.
- Religious groups such as Muslims for whom surgery may impact on religious practices and cause particular distress.

Because the Committee recommended TNF-alpha inhibitors for all patients, in line with their marketing authorisations, it did not consider that this issue warranted further discussion. Therefore this was not considered an equalities issue in this appraisal. No other equality issues were raised during the development of the original guidance.

GE paper sign off: **Helen Knight, 21/06/2018**

Contributors to this paper:

Information Specialist: Tom Hudson

Technical Analyst: Irina Voicechovskaja / Julia Sus

Associate Director: Sheela Upadhyaya

Project Manager: Emily Richards / Andrew Kenyon

Confidential information has been removed. © NICE 2018. All rights reserved. Subject to Notice of rights.

Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of infliximab, adalimumab and golimumab within their licensed indications for treating moderately to severely active ulcerative colitis.

6. Current guidance

1.1 Infliximab, adalimumab and golimumab are recommended, within their marketing authorisations, as options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.

Golimumab is recommended only if the company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, as agreed in the patient access scheme.

1.2 The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).

1.3 Infliximab is recommended, within its marketing authorisation, as an option for treating severely active ulcerative colitis in children and young people aged 6–17 years whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.

1.4 Infliximab, adalimumab or golimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Specialists should then discuss the risks and benefits of continued treatment with the patient, and their parent or carer if appropriate:

They should continue treatment only if there is clear evidence of response as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. People who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.

They should consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People whose disease relapses after treatment is stopped should have the option to start treatment again.

Confidential information has been removed. © NICE 2018. All rights reserved. Subject to Notice of rights.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

See Appendix C, section 3.

Confidential information has been removed. © NICE 2018. All rights reserved. Subject to Notice of rights.

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 specific 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

Confidential information has been removed. © NICE 2018. All rights reserved. Subject to Notice of rights.

Appendix B

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).	No
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.	Yes
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.

Confidential information has been removed. © NICE 2018. All rights reserved. Subject to Notice of rights.

1. Appendix C – other relevant information Relevant Institute work

Published

Inflammatory bowel disease (2015) NICE quality standard QS81

Ulcerative colitis: management (2013) NICE guideline CG166

Vedolizumab for treating moderately to severely active ulcerative colitis (2015) NICE technology appraisal guidance TA342

Ulcerative colitis: budesonide multimatrix (Cortiment) (2015) NICE evidence summary ESNM56

In progress

Ulcerative Colitis (update) NICE guideline. Publication date to be confirmed.

Tofacitinib for moderately to severely active ulcerative colitis. NICE technology appraisal guidance [ID1218]. Publication date to be confirmed.

2. Details of new products

See table on next page.

Confidential information has been removed. © NICE 2018. All rights reserved. Subject to Notice of rights.

Appendix D

Drug (company)	Details (phase of development, expected launch date)[2]	[redacted]
Filgotinib (Gilead)	Phase III for ulcerative colitis (UC).	[redacted]
Cobitolimod (InDex)	Failed to meet primary end point in a phase III study of third-line treatment of refractory UC in 2016. Following further analysis a phase IIb study using higher and more frequent doses is now planned.	[redacted]
Etrolizumab (Roche)	Phase III in people with UC who haven't previously used TNF inhibitors and whose disease is refractory to or intolerant of prior immunosuppressant and/or corticosteroid treatment. Regulatory filings expected in 2019.	[redacted]
Alicaforsen (Atlantic Healthcare)	Phase II for the second-line treatment of distal UC.	[redacted]
Ozanimod (Receptos)	Phase II (EU) / III (US) for moderate-to-severe, active UC	[redacted]
Tofacitinib (Pfizer)	Phase III for acute and maintenance treatment of moderate-to-severe ulcerative colitis	[redacted]
Ustekinumab (Janssen)	Phase III for moderate-to-severe active UC in adults	[redacted]
Mongersen (Celgene)	Phase II for UC	[redacted]

Confidential information has been removed. © NICE 2018. All rights reserved. Subject to Notice of rights.

Vedolizumab (Takeda)	New subcutaneous formulation. Phase III for inflammatory bowel disease, including UC.	[redacted]
Adalimumab biosimilars (various)	Several adalimumab biosimilars have been granted EU marketing authorisations in 2017.	[redacted]

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Infliximab *"Treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies"* and… *"Treatment of severely active ulcerative colitis, in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies"* Price: £419.62 for a 100 mg vial containing powder for reconstitution (excluding VAT; BNF edition 67)	No change to proposed indication. Price: currently ranges from £419.62 to £377 for a 100 mg vial containing powder for reconstitution, depending on whether the reference version of infliximab or biosimilar versions are used. The quoted prices exclude VAT [BNF Online https://bnf.nice.org.uk; accessed 20th November 2017]
Adalimumab	

[2] Information from NHS Specialist Pharmacy Service [https://www.sps.nhs.uk; accessed 20th November 2017] unless otherwise stated.

Confidential information has been removed. © NICE 2018. All rights reserved. Subject to Notice of rights.

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
"Treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies" … Price: £352.14 for a pre-filled 40 mg pen or syringe, or a 40 mg/0.8 ml vial (excluding VAT; 'British National Formulary' [BNF] edition 67).	No change to proposed indication. No change to price [BNF Online https://bnf.nice.org.uk; accessed 20th November 2017]. No NHS list prices are currently available for adalimumab biosimilars.
Golimumab *"Treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies"* Price: The list price of golimumab was £762.97 for a pre-filled 50 mg pen or syringe and £1525.94 for a 100 mg pre-filled pen (excluding VAT; BNF edition 67). Merck Sharp & Dohme agreed a patient access scheme with the Department of Health to make the 100 mg dose of golimumab available to the NHS at the same cost as the 50 mg dose.	No change to proposed indication. No change to list prices [BNF Online https://bnf.nice.org.uk; accessed 20th November 2017].

Confidential information has been removed. © NICE 2018. All rights reserved. Subject to Notice of rights.

4. 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 in October 2014
Efficacy and Safety of Adalimumab in Pediatric Subjects With Moderate to Severe Ulcerative Colitis NCT02065557; M11-290; 2013-003032-77	Adalimumab vs. placebo n = 245 Currently recruiting Estimated completion date: May 2021 (primary outcome); July 2021 (overall)
A Multi-Center, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate Long-Term Safety and Tolerability of Repeated Administration of Adalimumab in Pediatric Subjects with Ulcerative Colitis Who Completed the Study M11-290 (see above) 2015-001346-29; M10-870	Ongoing n = 93 Estimated completion date: not explicitly stated. Participants are followed for up to 96 weeks
An Efficacy and Safety Study of Vedolizumab Intravenous (IV) Compared to Adalimumab Subcutaneous (SC) in Participants With Ulcerative Colitis NCT02497469; MLN0002-3026; U1111-1168-6713; 2015-000939-33; NL54690.056.15	n = 770 Ongoing Estimated completion date: January 2019
A Study Comparing the Efficacy and Safety of Etrolizumab to Infliximab in Participants With Moderate to Severe Ulcerative Colitis Who Are Naive to Tumor Necrosis Factor Inhibitors NCT02136069; GA29103; 2013-004282-14	n = 720 Currently recruiting Estimated completion date: March 2023

Confidential information has been removed. © NICE 2018. All rights reserved. Subject to Notice of rights.

Trial name and registration number	Details
GIS-SUSANTI-TNF-2015 (Anti-TNF Discontinuation) NCT02994836	Placebo-controlled infliximab discontinuation study in people with either UC or Crohn's disease n = 300 Not yet open for recruitment Estimated completion date: December 2018 (primary outcome); December 2019 (overall)
A Randomized, Multicenter Open Label Study Comparing Early Administration of Azathioprine Plus Infliximab to Steroids Plus Azathioprine for Acute Severe Colitis NCT02425852; GETAID 2015-02; ACTIVE	n = 150 Current status unknown Estimated completion date: September 2017 (primary outcome); March 2018 (overall)
A study to evaluate the safety of stopping versus continuing anti TNF therapy in ulcerative colitis patients in remission, and to evaluate the safety and efficacy of restarting anti TNF therapy in patients with disease recurrence 2016-001409-18; HMR2016-0.6; Biostop study	Trial of adalimumab or infliximab discontinuation and restarting. n = 200 Ongoing Estimated completion date: December 2022

Appendix D – References

1. Travis, S (2017) Effect of Adalimumab on Clinical Outcomes and Health-related Quality of Life Among Patients With Ulcerative Colitis in a Clinical Practice Setting: Results From InspirADA. *Journal of Crohn's & colitis* 11 (11): 1317-1325.

Confidential information has been removed. © NICE 2018. All rights reserved. Subject to Notice of rights.