Evidence Review for Prescribing Clinical Network

Treatment: Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy

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Summary page
In NICE technology appraisal guidance [TA329] 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.

The PCN member clinical commissioning groups are required to comply with recommendations in this technology appraisal within 3 months of its date of publication (end May 2015).
The TA329 guidance is summarised in this paper, the full version is available at: http://www.nice.org.uk/guidance/ta329

Place in therapy / treatment pathway NICE treatment pathways available at pathways.nice.org.uk/ulcerative-colitis
Local implementation diagram presented at foot of this paper.

Is monitoring for efficacy required? Monitoring by specialist in secondary care

Is monitoring for toxicity required? Monitoring by specialist in secondary care

Is dose titration required? Not required

Traffic light status - RED

Role of the specialist Monitor patient's response to treatment (clinical, biochemical and endoscopic) and communicate outcomes to commissioners so that continued funding can be considered if appropriate

Role of GP Be aware of side effects potential complications and report to specialist

Financial implications

Estimated cost per 100 000 population:
NICE estimates an additional 22 patients per 100 000 population:
Drug costs per treatment cycle in adults - TNF–alpha inhibitors

Product	mg	Cost per unit (£)	Induction Units	Maint Units	Induction £	Maint £
Infliximab vial – proprietary [a]	100	419.62	12	13	5035	5455
Infliximab vial – biosimilars [b]	100	377.66	12	13	4532	4910
Adalimumab prefilled pen/ syringe [c]	40	352.14	8	13	2817	5306
Golimumab prefilled pen/syringe [d]	50 or 100	762.97	4	6.5	3052	4959

a The purchase price of proprietary infliximab may change as a consequence of the availability of biosimilars.
b There are two biosimilars for infliximab – Inflectra and Remsima. The cost shown is the NHS list price for Remsima. Costs may vary locally depending on local contractual arrangements.
c Maintenance doses of adalimumab (40 mg) may in some cases be used each week, as opposed to every 2 weeks (the standard regimen). Based on a response to the consultation it has been assumed that 15.9% of people receiving adalimumab are treated every week. Costs vary depending the dose prescribed, and.the above costs for adalimumab have been weighted to reflect this.
d The guidance recommends two different doses of golimumab - 50 mg and 100 mg. The company provides the higher dose at the same price as the 50 mg dose, as agreed in a patient access scheme. An induction period of 8 weeks has been shown here to allow comparison of costs between treatments, but this may vary depending on response.
All costs shown are based on the dose for an adult of 77kg. Costs are based on the structure used within the health economic analysis developed to inform the guidance.
All induction cycles last for 8 weeks, with maintenance cycles lasting 26 weeks.

The increased efficacy of TNF–alpha inhibitors is expected to delay or avoid costs associated with surgery (colectomy). The rate at which people with ulcerative colitis progress to colectomy surgery is not known due to a lack of data.

The estimated average total cost of surgery, including the costs of colectomy, ileoanal pouch formation, assessment under anaesthesia and complications is £12,900. The average cost of additional care after treatment is estimated at £2300 per annum.

Other issues None

National Guidance available: NICE TA329 guidance

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
V1	20.03.2015	Liz Clark	For comment	
V2	29.04.2015	Liz Clark	For PCN	Comments received from Dr Moodie (Epsom and St Helier) and Dr Ansari (Surrey and Sussex) resulting in updated flow chart and tick box form

1. Purpose of the Review

The PCN member clinical commissioning groups are required to comply with recommendations in NICE technology appraisal guidance [TA329] within 3 months of its date of publication, by end May 2015.
In the TA, 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.

Clinical need and practice

Ulcerative colitis is a chronic condition in which inflammation develops in the large intestine. Its exact cause is unknown although hereditary, infectious and immunological factors have been proposed as possible causes. Symptoms vary according to the extent and severity of the disease and may include bloody diarrhoea, abdominal pain, weight loss, fatigue, anaemia and an urgent need to defaecate. Some patients may also have extra‑intestinal manifestations involving joints, eyes, skin and liver. Symptoms can flare up then disappear for months or even years, but approximately 50% of patients with ulcerative colitis will relapse at least once a year. Ulcerative colitis can cause complications such as primary sclerosing cholangitis (inflamed and damaged bile ducts), bowel cancer, osteoporosis and toxic megacolon (swelling of the colon caused by trapped gases, which can be life‑threatening).

Ulcerative colitis can develop at any age but the peak incidence is between 15 and 25 years of age with a second, smaller peak between 55 and 65 years. It is estimated that approximately 128,400 people in England have ulcerative colitis. Around 80% of the people affected have mild or moderate disease and 20% have severe disease.

The modified Truelove and Witts severity index is widely used to classify the severity of ulcerative colitis. It defines mild ulcerative colitis as fewer than 4 bowel movements daily; moderate ulcerative colitis as more than 4 daily bowel movements but the patient is not systemically ill; and severe ulcerative colitis as more than 6 bowel movements daily and the patient is also systemically ill (as shown by tachycardia, fever, anaemia or a raised erythrocyte sedimentation rate). Severe ulcerative colitis, as defined by the Truelove and Witts severity index, is potentially life threatening and normally requires hospitalisation and emergency care. This is aligned with the UK definition of 'acute severe ulcerative colitis'. NICE's guideline on ulcerative colitis equates 'subacute ulcerative colitis' to moderately to severely active ulcerative colitis, which would normally be managed in an outpatient setting and does not require hospitalisation or the consideration of urgent surgical intervention. This appraisal includes moderately to severely active ulcerative colitis but not acute severe ulcerative colitis (that is, severe ulcerative colitis according to the Truelove and Witts severity index). Recommendations for treating acute severe ulcerative colitis can be found in NICE's guideline on managing ulcerative colitis and NICE's technology appraisal guidance on infliximab for acute exacerbations of ulcerative colitis.

Treatment for ulcerative colitis aims to relieve symptoms during a flare-up and then to maintain remission. The management of moderately to severely active ulcerative colitis involves treatment with oral or topical aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine), or with corticosteroids if aminosalicylates are contraindicated or not tolerated. Oral corticosteroids or drugs that affect the immune response can also be added if the disease does not respond to aminosalicylates. Colectomy is a treatment option if symptoms are inadequately controlled or if the patient has a poor quality of life on conventional therapy.

Summary of the NICE TA Guidance

Infliximab, adalimumab and golimumab are recommended, within their marketing authorisations, as options for treating moderately to severely active ulcerative colitis (Mayo score > 6) 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.

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).

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.

Most likely cost-effectiveness estimate (given as an ICER)

In the company's model for adalimumab, the base-case ICER for adalimumab compared with conventional therapy was £34,400 per QALY gained. This was revised to £23,000 per QALY gained; a revision not critiqued by the Assessment Group.

When the Assessment Group compared medical options only, infliximab was dominated by adalimumab, and golimumab was extendedly dominated by adalimumab and conventional therapy.
The base-case ICER for adalimumab compared with conventional therapy was £50,600 per QALY gained.

The Committee concluded that the economic analysis had tended to underestimate the cost effectiveness of TNF-alpha inhibitors.

Not covered in NICE TA

NICE do not define what conventional therapy should look like; just that it includes corticosteroids and mercaptopurine or azathioprine.

Would adequate conventional therapy include;
Aminosalicylate (5ASA) drugs used at sufficient doses (e.g. Mesalazine 4.8g per day orally or 1g PR),
Thiopurines (azathioprine or mercaptopurine) – at adequate doses (2-2.5mg/kg), checking adherence to tablets and dose optimisation using metabolite (6-TGN & 6-MMP) testing and adding allopurinol if appropriate to reduce hepatotoxicity.
Tacrolimus or ciclosporin – with monitoring and dose adjustment as required.

Adjusting disease modifying drugs according to patient response and blood tests can result in reduced total drug use and improved patient experience.

NICE do not explicitly define moderately to severely active Ulcerative Colitis, however the trials included use the Mayo Score of 6 to 12.
The trials define clinical response as a reduction in Mayo score of >3 points and of >30% with a reduction in rectal bleeding.
The trials define remission as a Mayo score of two or less with no subscore of over one.