NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262)

Final scope

Remit/appraisal objective

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

Background

Ulcerative colitis is a chronic condition where inflammation develops in the large intestine. Symptoms include bloody diarrhoea, abdominal pain, weight loss, fatigue, anaemia and an urgent need to defaecate. These vary according to the extent and severity of the inflammation. Symptoms can flare up and then disappear for months or even years, but approximately 50% of people with ulcerative colitis will relapse at least once a year. Common complications of ulcerative colitis include primary sclerosing cholangitis (inflamed and damaged bile ducts), bowel cancer, osteoporosis and toxic megacolon (trapped gases in the colon, causing it to swell). Severe ulcerative colitis, in particular, is also associated with significant emotional distress.

Ulcerative colitis has a reported annual incidence in the UK of approximately 10 per 100,000 people, and a prevalence of approximately 240 per 100,000. Therefore, it is estimated that approximately 132,600 people in England and Wales are diagnosed with ulcerative colitis. About 80% of all incident cases of ulcerative colitis are mild or moderate in severity. The age of onset peaks between 15 and 30 years of age but the disease may present at all ages.

The modified Truelove and Witts severity index is widely used to classify the severity of ulcerative colitis: mild ulcerative colitis is defined as fewer than 4 bowel movements daily, moderate ulcerative colitis is defined as more than 4 daily bowel movements but where the patient is not systemically ill, and severe ulcerative colitis is defined as more than 6 bowel movements daily, and when the patient is also systemically ill as shown by tachycardia, fever, anaemia or a raised erythrocyte sedimentation rate. The modified Truelove and Witts definition of severe ulcerative colitis, which is potentially life threatening, is in line with the UK definition of acute severe ulcerative colitis. NICE clinical guideline 166 ‘Ulcerative colitis: Management in adults, children and young people’ recognises “subacute ulcerative colitis” as moderately to severely active ulcerative colitis that would normally be managed in an outpatient setting and does not require hospitalisation or the consideration of

urgent surgical intervention. The scope of this appraisal includes people with moderately to severely active ulcerative colitis (including subacute disease) but does not include acute severe ulcerative colitis. NICE recommendations for the management of acute severe ulcerative colitis are covered by CG166 and NICE technology appraisal 163 (infliximab for acute exacerbations of ulcerative colitis).

There is no cure for ulcerative colitis. The aim of treatment is to relieve symptoms during a flare-up and to maintain remission thereafter. Management of mildly to moderately active colitis involves treatment with, oral or topical aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine) or corticosteroids when aminosalicylates are contraindicated or not tolerated. Oral corticosteroids or oral immunosuppressants are also added on if the disease does not respond to treatment with aminosalicylates. NICE does not recommend infliximab for treating 'subacute' manifestations of moderately to severely active ulcerative colitis (NICE technology appraisal guidance 140). NICE was unable to appraise adalimumab for treating moderately to severely active ulcerative colitis because the manufacturer did not provide an evidence submission (NICE technology appraisal guidance 262). Colectomy is a treatment option if symptoms are inadequately controlled or the patient has a poor quality of life on conventional treatment.

The technologies

Infliximab (Remicade, Merck Sharp & Dohme) is a chimeric monoclonal antibody that binds with high affinity to TNF-alpha, thereby neutralising its activity. It is administered by intravenous infusion. Infliximab has a UK marketing authorisation for the 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. Infliximab also has a UK marketing authorisation for the 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. Biosimilar versions of infliximab (Remsima, Celltrion Healthcare; Inflectra, Hospira) have been licensed for the same indications.

Adalimumab (Humira, AbbVie) inhibits the activity of TNF-alpha. It is a fully human recombinant monoclonal IgG1 antibody specific for TNF-alpha. It is administered by subcutaneous injection. Adalimumab has a UK marketing authorisation for the 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.

Golimumab (Simponi, Merck Sharp & Dohme) is a fully humanised monoclonal antibody that inhibits TNF-alpha. It is administered

subcutaneously. Golimumab has a UK marketing authorisation for the 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.

Intervention(s)	For adults: • adalimumab • infliximab • golimumab For children and adolescents: • infliximab
Population(s)	People with moderately to severely active ulcerative colitis (excluding those with acute severe ulcerative colitis, as defined in the background section), whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant of or have medical contraindications to such therapies
Comparators	Adalimumab, infliximab and golimumab should be compared with each other and with standard clinical management which may include a combination of aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine), corticosteroids (beclomethasone, budesonide, hydrocortisone or prednisolone), and thiopurines (mercaptopurine or azathioprine), calcineurin inhibitors and surgical intervention

Outcomes	The outcome measures to be considered include: • mortality • measures of disease activity • rates of and duration of response, relapse and remission • rates of hospitalisation • rates of surgical intervention • time to surgical intervention • adverse effects of treatment (including leakage and infections following surgery) • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.
Other considerations	If evidence allows, subgroup analysis of patients based on duration of disease will be considered. Guidance will only be issued in accordance with the marketing authorisation.

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 140, April 2008, 'Infliximab for subacute manifestations of ulcerative colitis'. Technology Appraisal No. 163, December 2008, 'Infliximab for the treatment of acute exacerbations of ulcerative colitis'. Terminated Technology Appraisal No. 262, July 2012, 'Adalimumab for the treatment of moderate to severe ulcerative colitis'. Proposed Technology Appraisal, 'Vedolizumab for treating moderately to severely active ulcerative colitis'. Publication TBC. Related Guidelines: Clinical Guideline No. 166, June 2013, 'Ulcerative colitis: Management in adults, children and young people'. Related Quality Standards: Quality Standard in Preparation, 'Inflammatory bowel disease (to cover Ulcerative colitis and Crohn's disease)', Anticipated date of publication September 2014. http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp Related NICE Pathways: NICE Pathway: Ulcerative colitis overview, Pathway created: June 2013. http://pathways.nice.org.uk/pathways/ulcerative-colitis