Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Infliximab for the treatment of acute exacerbations of ulcerative colitis

Draft scope

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.[1]

Background

Ulcerative colitis (UC) is a chronic condition in which there is inflammation of the mucosa of the large intestine. The cause of ulcerative colitis is unknown. Hereditary, infectious and immunological factors have been proposed as possible causes.

The incidence of UC is approximately 10-20 per 100,000 per year with a reported prevalence of 100-200 per 100,000 in the UK. This prevalence is likely to be an underestimate as this implies an average disease duration of 10 years for a condition that is known to last for life. Based on these prevalence figures there are between 52,794 – 105,587 people in England and Wales with UC. The age of onset peaks between 20 and 40 years of age but the disease may present at all ages. The prevalence of UC in children is about 6 to 7 per 100,000 in the UK.

The symptoms of UC vary according to the extent and severity of the inflammation. The classic symptom of UC is bloody diarrhoea. Associated symptoms of colicky abdominal pain, urgency, or tenesmus may be present. Mildly active UC is defined as less than four bowel movements daily. Moderately active UC is defined as more than four daily bowel movements but where the patient is not systemically ill. Severe UC is defined as an attack in which the patient has more than six bowel movements daily, and who is systemically ill as shown by tachycardia, fever and anaemia. Fulminant disease correlates with more than ten bowel movements daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement and colonic dilation (expansion). Patients in this category may have inflammation extending beyond just the mucosal layer, causing impaired colonic motility and leading to toxic megacolon (toxic dilation of the colon).

[1] The Department of Health and Welsh Assembly Government remit to the Institute: To appraise the clinical and cost effectiveness of infliximab for ulcerative colitis.

Approximately 90% of all incident cases of UC are mild or moderate in severity.

In UC the severity of the symptoms fluctuate unpredictably over time with intervals of remission or reduced symptoms. Approximately 50% of patients with UC have a relapse in any year. A significant minority have frequently relapsing or chronic, continuous disease. Twenty-five percent of patients with severe UC are admitted to an in-patient setting with flares of UC that are not responding to steroids. An estimated 20-30% of patients with pancolitis (disease affecting the entire colon) will require colectomy.

Complications of UC may include haemorrhage, perforation, stricture formation, abscess formation, anorectal disease (e.g. fissures), arthritis, eye, cutaneous and liver abnormalities. Patients with long-standing dysplasia and extensive colitis have an increased risk of bowel cancer. UC has a slight excess of mortality in the first two years after diagnosis, but little subsequent difference from the general population. A severe attack of UC is a potentially life threatening illness.

The British Society of Gastroenterology published guidelines for the treatment of UC in 2004. The main recommendations for the medical management of severe UC indicate that patients who have failed to respond to oral treatment combination of mesalazine and/or steroids should be admitted for intensive intravenous therapy. When hospitalised patients usually are given intravenous corticosteroids and, if no or merely partial improvement after 3 days, surgical intervention or intravenous ciclosporin is considered. Following induction of remission, patients with UC should normally receive maintenance therapy with aminosalicylates, azathioprine, mercaptopurine or ciclosporine to reduce the risk of relapse. Patients frequently receive combination therapies. Severe UC should be managed jointly by a gastroenterologist in conjunction with a colorectal surgeon.

The technology

Infliximab (Remicade, Schering Plough) is a chimeric monoclonal antibody that binds with high affinity to TNF-alpha, thereby neutralising its activity. It is administered by intravenous infusion and is licensed for use in rheumatoid arthritis, active Crohn’s disease, psoriasis, psoriatic arthritis and ankylosing spondylitis as well as UC.

Infliximab is licensed for moderately to severely active UC in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies.

Intervention(s)	Infliximab.
Population(s)	Adults with acute exacerbations of severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies, and whose clinical management require hospitalisation.
Standard comparators	The standard comparators to be considered include: • standard clinical management which may include surgical intervention • ciclosporin.
Outcomes	The outcome measures to be considered include: • health-related quality of life • survival • rates of surgical intervention • measures of disease activity • rates of and duration of response, relapse and remission • adverse effects of treatment.
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. Time horizon should be long enough to allow reasonable estimation of expected costs (including adverse events if applicable) and benefits for the intervention, but should also account for the disease specific feature, particularly fluctuation and unpredictability of symptoms. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	Where evidence permits, the appraisal of infliximab for the acute exacerbation of severely active UC should identify patient subgroups for whom the technology is most appropriate. Where evidence permits, the appraisal of infliximab for the acute exacerbation of severely active UC should consider different posology or methods of administration, treatment continuation strategies and lengths of treatment required when patients have responded to infliximab. Guidance will only be issued in accordance with the Summary of Product Characteristics
Related NICE recommendations	Related ongoing Technology Appraisals: Infliximab for the sub-acute manifestation of ulcerative colitis. Expected publication date: April 2008. Related Guidelines: None

Questions for consultation

1. Does the treatment pathway described in the draft scope represent the experience of clinical practice? Is, for example, infliximab in the acute setting of the disease, for patients who have been hospitalised due to the acute exacerbation of UC, expected to be administered after a 3-day intravenous course of corticosteroids with the aim of avoiding or delaying surgical intervention and inducing remission?

2. While acknowledging eventual data limitations, should the economic analysis focus only on the immediate avoidance of surgical intervention, or should the appraisal take in consideration both the immediate avoidance or surgery and long term impact in terms of remission?