NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Use of tumour necrosis factor alpha (TNF α) inhibitors (adalimimab, certolizumab and infliximab [review]) and natalizumab for Crohn's disease

Draft scope

Appraisal objective

To appraise the clinical and cost effectiveness of the tumour necrosis factor alpha (TNF α) inhibitors and natalizumab within their licensed indications for Crohn's disease.

Background

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract that may affect any part from the mouth to the anus but has a particular tendency to affect the terminal ileum and ascending colon (ileocolonic disease). People with Crohn's disease have recurrent attacks, with acute 'flares' of the disease interspersed with periods of remission or less active disease. These 'flares' may affect any part of the gastrointestinal tract. It may be defined by location (terminal ileal, colonic, ileocolic, upper gastrointestinal), or by the pattern of the disease (inflammatory, fistulating, or stricturing).

Crohn's patients symptoms include diarrhoea, abdominal pain and weight loss, constitutional symptoms include malaise, lethargy, anorexia, nausea, vomiting and low grade fever may be present.

Crohn's disease can be complicated by the development of intestinal obstruction, fistulae and perianal disease. Fistulae develop in about one third of patients. Perianal disease is a frequent complication of colonic and ileocolonic disease and is characterised by fissures, fistulae and abscesses.

The prevalence of Crohn's disease is estimated to be about 50-100 per 100,000 in the population. The incidence of Crohn's disease is greatest in people aged between 10 and 40 years. However, it may affect people of any age and 15% of people are over the age of 60 at diagnosis.

A number of activity indices have been developed. The Crohn's Disease Activity Index (CDAI) is one of the most frequently used indices in assessing the severity of the disease. The other commonly used index is the Harvey-Bradshaw index which correlates well with CDAI.

Crohn's disease is neither medically nor surgically curable. Treatment is aimed at inducing remission, preventing relapses, improving quality of life and addressing complications. Treatment options include drug therapy, attention to nutrition and, in severe or active disease, surgery. Drug therapy may include corticosteroids (budesonide, hydrocortisone and prednisolone), 5-

aminosalicylate (5-ASA), immunosuppressive drugs (azathioprine), antimetabolites (6-mercaptopurine and methotrexate) and antibiotics. Tumour necrosis factor alpha (TNF-a) inhibitors (adalimimab, certolizumab and infliximab) and natalizumab may be used in some people with severe disease.

Management is determined by severity of the disease, taking into account: the site (ileal, ileocolonic, colonic, other), pattern (inflammatory, structuring, fistulating) and activity of the disease. At least 50% of patients require surgical treatment in the first 10 years of disease and approximately 70-80% will require surgery within their lifetime. The overall mortality of Crohn's disease is slightly higher than the normal population and is greatest in the 2 years after diagnosis or in those with upper gastrointestinal disease.

The technologies

Adalimumab (Humira, Abbott Laboratories) is a fully human anti-TNF-α monoclonal antibody. It is administered by subcutaneous injection. Adalimumab is not currently licensed for the treatment of Crohn's disease. It is currently being used in clinical trials for the induction and maintenance of clinical remission and response in patients with moderate to severely active Crohn's disease.

Certolizumab Pegol (Cimzia, UCB) is a PEGylated FAB fragment of a humanised anti-TNF-α monoclonal antibody which binds with high affinity to TNF-α, inhibiting its activity. Certolizumab Pegol is not currently licensed for the treatment of Crohn's disease. It is currently being used in clinical trials for the induction and maintenance of clinical remission and response in patients with moderate to severely active Crohn's disease

Infliximab (Remicade, Schering-Plough) is a humanised anti-TNF-α monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF-α, inhibiting its activity. It is licensed for the management of severe active Crohn's disease in patients whose condition has not responded adequately to treatment with a corticosteroid and a conventional immunosuppressant or who are intolerant of them and as maintenance therapy refractory fistulating Crohn's disease. It is also licensed for the management of rheumatoid arthritis, ulcerative colitis ankylosing spondyitis, psoriatic arthritis and psoriasis.

Natalizumab (Antegren, Biogen Idec/Elan) is a selective adhesive molecule (SAM) inhibitor. SAM inhibitors are designed to selectivity inhibit immune cells from leaving the blood stream and to prevent these cells from migrating into chronically inflamed tissue where they may cause or maintain inflammation. Natalizumab is not currently licensed for the treatment of Crohn's disease. It is currently being used in clinical trials in patients with moderate to severely active Crohn's disease.

Interventions	Adalimumab, certolizumab pegol, infliximab and natalizumab within their licensed indications.
Population(s)	• People with moderate to severe active Crohn's disease who are intolerant of, or whose condition has not responded adequately to, conventional treatment. • People with refractory fistulating Crohn's disease (infliximab only).
Standard comparators	• Conventional treatment strategies without natalizumab or TNF-α inhibitors (including no treatment, dietary intervention, drug treatment with aminosalicylates, corticosteroids [prednisolone, budesonide and hydrocortisone], azathioprine, metronidazole, or surgical intervention) • TNF-α inhibitors • Natalizumab
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • health-related quality of life • disease activity (remission, response, relapse) • need for surgery • 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. The economic evaluation should be based on an appropriate time horizon over which the main costs and benefits can reasonably be expected given the chronic nature of the condition. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	Guidance will only be issued in accordance with the Summaries of Product Characteristics. If evidence allows considering the different dosing schedules of the treatment and the effects this has on the clinical and economic outcomes. If evidence allows consideration will be given to subgroups in whom the treatments may be particularly appropriate. Disease activity in Crohn's will be defined using specified indices including the Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw index.
Related NICE recommendations	Technology appraisal guidance no. 40. The clinical effectiveness and cost effectiveness of infliximab for Crohn's Disease: March 2002

Questions for consultation

Is the target population defined appropriately?

Is it appropriate to compare the treatments of interest with conventional therapy? Which of the treatments listed are the most commonly used for the treatment of moderate to severe Crohn's disease in UK practice?

Should maintenance therapy be considered separately from induction of remission?