NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Darvadstrocel for treating complex perianal fistula in Crohn's disease

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of darvadstrocel within its marketing authorisation for treating perianal fistula in Crohn's disease.

Background

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract (gut) that may affect any part of the gut from the mouth to the anus. People with Crohn's disease have acute exacerbations ('flares') in between periods of remission or less active disease. These flares may affect any part of the gut and are defined by location (terminal ileal, colonic, ileocolic, upper gastrointestinal), or by the pattern of the disease (inflammatory, fistulising, or stricturing). Luminal Crohn's disease affects the lining of the intestine.

Inflammation of the gut can lead to tissue damage and ulceration. A complication of such tissue damage is the development of fistula. A perianal fistula is an abnormal connection that develops between the bowel and the skin near the anus. The symptoms of perianal fistula include skin irritation around the anus, pain, passing of blood or pus when having a bowel movement and leakage of faecal matter. Fistulas are described as simple or complex depending on the location and whether there is a singular fistula tract or interlinking connections.

There are currently at least 115,000 people in the UK with Crohn's disease.[i] The incidence of Crohn's disease is greatest in people aged between 16 and 30 years. However, it may affect people of any age. Approximately 20% of people with Crohn's disease will develop a perianal fistula, and 30% of these people have recurrent fistulas.[1]

Treatments for perianal fistula aim to treat and drain the underlying infection and heal the fistula. Medications for treating fistulas can include antibiotics, immunosuppressants (such as azathioprine or mercaptopurine) or biological treatments (such as infliximab and adalimumab). For some people surgery is needed. Following drainage of the infection, types of surgery may include use of a seton (in which a piece of thread is passed through the fistula and tied in a loop); fistulotomy (involving surgically opening the tract to allow the tissues to heal from the inside out); advancement flap procedures (attachment of a piece of rectal or anal tissue over the internal opening of the fistula following fistulotomy) or use of biosynthetic plugs to block the internal opening of the fistula. Fibrin glue is a non-surgical option for treating an anal fistula. The fibrin glue is injected into the fistula to seal the tract.

NICE guidance is available for some, but not all, current treatments for perianal fistula. NICE technology appraisal 187 recommends the anti-tumour necrosis factor (TNF) inhibitors infliximab and adalimumab as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. Technology appraisal guidance 187 further recommends infliximab as a treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy. Interventional procedures guidance 410 recommends that there are no major safety concerns with using a suturable biosynthetic plug to block the internal opening of the fistula. However, data on the efficacy of this procedure is limited and the guidance states that the procedure should only be used with special arrangements for clinical governance, consent and audit or research.

The technology

Darvadstrocel (Alofisel, Takeda) is a suspension of expanded human adipose-derived stem cells of allogeneic origin (adipose-derived stem mesenchymal stem cells). These stem cells have the potential to regulate the function of immune-cells including B lymphocytes, T-lymphocytes, NK cells, monocyte –derived dendritic cells, and neutrophils. Darvadstrocel is administered by a single injection into the fistula

Darvadstrocel does not currently have a marketing authorisation in the UK for treating complex perianal fistula in Crohn's disease. It has received its Committee for Medicinal Products for Human Use positive opinion for the treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy. Darvadstrocel should be used after conditioning of the fistula. In clinical trials two weeks before treatment administration, all patients underwent examination under anaesthetic, and fistula curettage was performed. If indicated, a seton was placed.

Intervention(s)	Darvadstrocel
Population(s)	Adult with non-active/mildly active luminal Crohn's disease, with complex perianal fistulas which have shown an inadequate response to at least one conventional or biologic therapy.
Comparators	Surgical management without darvadstrocel

Outcomes	The outcome measures to be considered include: • closure of fistula • recurrence of fistula • continence • mortality • adverse effects of treatment • 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
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If evidence allows patients with perianal-limited disease will be considered.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Infliximab and adalimumab for the treatment of Crohn's disease' (2010). NICE Technology Appraisal 187. On static list. 'Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy' (2015) NICE Technology Appraisal 352. Review date August 2018 'Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy' (2017) NICE technology appraisal 456. Related Guidelines: 'Crohn's disease: management' (2012). NICE guideline 152 Review date December 2016. Related Interventional Procedures:

	'Closure of anal fistula using a suturable bioprosthetic plug' (2011). NICE interventional procedures guidance 410. Related NICE Pathways: Crohn's disease overview (2012). NICE pathway
Related National Policy	Department of Health, Manual for Prescribed Specialised Services 2013/14, Jan 2014. Chapter 101 Severe intestinal failure service (adults) Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domain 2. NHS England (2013) 2013/14 NHS standard contract for colorectal: complex inflammatory bowel disease (adult). Service Specification Number: A08/S/c

References

1. Gecse K, Bemelman W, Kamm M et al (2014) A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut 63:1381-1392