Infliximab (Remicade) for paediatric ulcerative colitis - second line

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Infliximab (Remicade) for paediatric ulcerative colitis - second line

Target group
- Ulcerative colitis (UC) in children aged 6-17 years: moderate to severe – second line after failure of conventional therapy.

Technology description
Infliximab (Remicade) is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of tumour necrosis factor-α (TNF-α), neutralising its biological effects. Infliximab is administered intravenously at a dose of 5mg/kg in weeks 0, 2 and 6, and every 8 weeks thereafter.

Infliximab is licensed in the EU for:
- Ulcerative colitis – treatment of moderately to severely active disease in adult 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.
- Adult Crohn’s disease:
  - Treatment of moderately to severely active Crohn's disease, in patients who have not responded to a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
  - Treatment of fistulising, active Crohn's disease, in patients who have not responded to conventional treatment (including antibiotics, drainage and immunosuppressive therapy).
- Paediatric Crohn’s disease – in children and adolescents aged 6-17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies.
- Rheumatoid arthritis – in combination with methotrexate for:
  - Adult patients with active disease when the response to disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, has been inadequate.
  - Adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.
- Ankylosing spondylitis – treatment of severe, active disease, in adult patients who have responded inadequately to conventional therapy.
- Psoriatic arthritis – treatment of active and progressive disease in adult patients with an inadequate response to previous DMARD therapy.
- Psoriasis – treatment of moderate to severe plaque psoriasis in adult patients who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

Common reported side-effects of infliximab include upper respiratory tract infections, headache, sinusitis, abdominal pain, nausea and infusion-related reactions.

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PUVA - Psoralen plus UVA phototherapy
Infliximab is also in phase III development for Crohn’s disease (prevention of relapse), treatment of hepatitis C infection (treatment naive patients), plaque psoriasis (in combination with methotrexate), ulcerative colitis (combination therapy), and phase II development for pyoderma.

**Innovation and/or advantages**
Infliximab represents the first licensed anti-TNF medication for the paediatric population, with moderate to severe disease, providing an additional treatment option where corticosteroids and other immunosuppressive agents are inadequate to control disease.

**Developer**
MSD/Janssen Biologics.

**Availability, launch or marketing dates, and licensing plans**
In phase III clinical trials.

**NHS or Government Priority Area**
None identified

**Relevant guidance**
- NICE technology appraisal in development. Ulcerative colitis (moderate to severe, second line) – adalimumab. Expected date of issue to be confirmed³.
- NICE technology appraisal. Infliximab for the treatment of acute exacerbations of ulcerative colitis. 2008⁴.
- NICE technology appraisal. Infliximab for subacute manifestations of ulcerative colitis. 2008⁵.
- NICE interventional procedure guidance. Leukapheresis for inflammatory bowel disease. 2005⁷.


**Clinical need and burden of disease**
UC is a form of chronic inflammatory bowel disease (IBD) affecting the colon and rectum. The most common symptoms are abdominal cramping, faecal urgency and bloody diarrhoea⁷. Patients with IBD are at an increased risk of developing colorectal cancer, thought to be the result of chronic inflammation of the gastrointestinal mucosa¹².
Patients with UC have approximately 20% lifetime risk of colorectal cancer, with the risk increasing with the duration of the disease. Colorectal cancer is rarely encountered in patients experiencing colitis for less than seven years. Thereafter the risk is estimated to increase at a rate of 0.5-1.0% per year. The clinical course of UC is marked by exacerbation and remission, with around 50% of patients experiencing a relapse in any year. Flare-ups can significantly affect patients’ quality of life; around 55% of patients report flare-ups every few months, 9% have monthly flare-ups, and a further 9% experience weekly problems.

A prospective survey of IBD in children aged under 16 years carried out in the UK and Ireland during 1998 and 1999 reported the incidence of UC in England and Wales as 1.4 and 1.7 per 100,000 per year respectively. A more recent prospective study of paediatric IBD conducted in South Wales over an eight year period (1996-2003) found the incidence of UC in children under 16 years of age to be 1.5 cases per 100,000 per year. The prevalence of paediatric IBD in South Wales has been reported as 20 per 100,000 childhood population (children aged 0-16 years) with a 3:1 preponderance of Crohn’s disease compared to UC. Although presentation of UC symptoms during adolescence is common, as many as 40% of children present before the age of 10.

In 2009-2010 there were 909 finished consultant episodes for UC in patients aged up to 14 years (inclusive) in England and a total of 34,096 admissions and 80,584 bed days within the total population (ICD10 K51). UC has a slight excess of mortality in the first two years after diagnosis, but little subsequent difference from the general population thereafter. A severe attack of UC can be potentially life threatening, however in England and Wales in 2009 there was only 1 registered death in patients aged up to 19 years (inclusive).

**Existing comparators and treatments**

Treatment of UC involves induction of remission in patients with active disease and subsequent maintenance of remission.

Paediatric treatments include:

- Aminosalicylates – mild to moderate UC. Available as oral preparations, retention enemas, rectal foam preparation and suppositories (examples include mesalazine, balsalazide sodium and sulphasalazine).
- Corticosteroids – moderate to severe relapsing UC. Available as oral preparations, parenteral preparations, retention enemas and rectal foam preparations (examples include prednisolone, beclometasone dipropionate, hydrocortisone).
- Unlicensed immunosuppressants are often used for second line treatment, including azathioprine (the most commonly used), 6-mercaptopurine, methotrexate and, rarely, tacrolimus. In severe acute UC, short-term ciclosporin (IV) is occasionally used in children not responding to IV corticosteroids.
- Trials of exclusive polymeric liquid diet – e.g. Modulen.
- Colectomy.

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b Expert personal communication
Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00336492, CR012388, C0168T72; children and adolescents; infliximab; phase III.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Centocor, Inc.</td>
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<tr>
<td>Status</td>
<td>Published in abstract.</td>
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<tr>
<td>Source of information</td>
<td>Abstract.</td>
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<tr>
<td>Location</td>
<td>EU, USA and Canada.</td>
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<td>Design</td>
<td>Randomised, dose-ranging.</td>
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<tr>
<td>Participants and schedule</td>
<td>n=60; children aged 6-17; moderately to severely active UC; receiving, failed to respond to, or adverse effects from aminosalicylates, immunomodulators or corticosteroids. Following induction regimen of infliximab 5mg/kg at week 0, 2 and 6, patients randomised to 5mg/kg every 8 weeks through week 46, or 5mg/kg every 12 weeks through week 42.</td>
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<td>Follow-up</td>
<td>Active treatment period 54 weeks.</td>
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<tr>
<td>Primary outcomes</td>
<td>Efficacy of induction regimen in inducing clinical response as measured by Mayo score; safety of infliximab during induction and maintenance dosing regimens.</td>
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<td>Secondary outcomes</td>
<td>Efficacy of maintenance regimens in maintaining remission as measured by Paediatric Ulcerative Colitis Activity Index (PUCAI) score; efficacy of induction regimen in inducing clinical remission as measured by Mayo and PUCAI score; efficacy of induction regimen in inducing mucosal healing.</td>
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<tr>
<td>Key results</td>
<td>At week 8, 73.3% of patients experienced a clinical response, 40% (Mayo score) and 33.3% (PUCAI score) experienced clinical remission, 68.3% achieved mucosal healing and 33.3% had normal or inactive disease as measured by endoscopy; at week 54, a greater proportion were in remission (PUCAI score) in the 5mg/kg every 8 weeks treatment group (38.1%) than in the 5mg/kg every 12 weeks treatment group (18.2%); no deaths, malignancies, serious neurologic events, opportunistic infections, tuberculosis or congestive heart failure were reported.</td>
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<td>Adverse effects (AEs)</td>
<td>Through week 54 the proportion of subjects experiencing serious AEs was similar across treatment groups; all subjects in both treatment groups reported one or more AEs; more subjects in the 5mg/kg every 12 weeks group discontinued treatment than the 5mg/kg every 8 weeks treatment group; similar numbers of subjects reported infections requiring oral or parenteral treatment across each group; antibodies to infliximab developed in 4 subjects.</td>
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Estimated cost and cost impact
The cost of infliximab for this indication is not yet known. However, the cost of infliximab 100mg vial for its licensed indications is £419.62.²²

Claimed or potential impact – speculative

Patients

- ☐ Reduced mortality or increased length of survival
- ☑ Reduction in associated morbidity or improved quality of life for patients and/or carers
- ☐ Quicker, earlier or more accurate diagnosis or identification of disease
- ☐ Other:
- ☐ None identified
Services

☑ Increased use: requirement for IV infusion.
☐ Service organisation
☐ Staff requirements

☐ Decreased use
☐ Other:
☐ None identified

Costs

☐ Increased unit cost compared to alternative
☐ Increased costs: more patients coming for treatment
☐ Increased costs: capital investment needed

☐ New costs:
☐ Savings:
☑ Other: Dependent upon dosing regimen.

Other issues

☐ Clinical uncertainty or other research question identified:
☐ None identified

References

3 National Institute for Health and Clinical Excellence. Ulcerative colitis (moderate to severe, second line) - adalimumab. Technology appraisal in development. Expected date of issue to be confirmed.

