Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

Re-Submission

Infliximab 100mg powder for concentrate solution for infusion (Remicade®)

SMC No. (374/07)

Merck, Sharp & Dohme Ltd

04 April 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

infliximab (Remicade®) is not recommended for use within NHS Scotland.

Indication under review: Treatment of moderately to severely active ulcerative colitis 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.

In two randomised controlled studies, infliximab 5mg/kg intravenous infusion on weeks 0, 2 and 6 was significantly superior to placebo for the endpoint of clinical response at week eight.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 12 May 2014

Indication

Treatment of moderately to severely active ulcerative colitis (UC) 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

Dosing Information

Infliximab 5mg/kg given as an intravenous infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. three doses. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Infliximab treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of inflammatory bowel diseases.

Product availability date

28 February 2006

Summary of evidence on comparative efficacy

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon characterised by mucosal ulceration, rectal bleeding, diarrhoea, and abdominal pain.[1] Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of tumour necrosis factor (TNF)α.[2] The submitting company has requested that SMC considers infliximab when positioned for use as an alternative to ciclosporin in adult patients with acute, severe UC (i.e. in the context of 'rescue therapy' as opposed to the maintenance phase of treatment). This reflects UK and European guidance.[3,4,5] Infliximab is also licensed for use in severely active UC in children and adolescents aged 6 to 17 years, where SMC accepted it for restricted use as an alternative to ciclosporin for rescue therapy.

One phase III randomised, open-label, comparative study of ciclosporin versus infliximab has been conducted in ciclosporin- and infliximab-naïve patients with an acute severe flare of UC (>10 on the Lichtiger scale, ranging from 0 to 21 points) and who had had an unsuccessful course of intravenous (iv) high-dose steroids.[1] The study was designed as a superiority study and the sample size of 100 patients was based on an assumption that failure rate would be 30% in the ciclosporin group (amended to 45% in planned interim analysis and sample size increased to 116 patients) and 60% in the infliximab group.

Patients were randomised equally on day 0 to ciclosporin 2mg/kg/day continuous iv infusion (dose adjusted to obtain a ciclosporin blood concentration between 150 to 250 nanograms/mL) or infliximab 5mg/kg iv infusion. On day seven, patients with a clinical response in the ciclosporin group were switched to oral ciclosporin 4mg/kg/day until day 98 and patients with a response in the infliximab group received two iv infusions of infliximab 5mg/kg on days 14 and 42 only. A clinical response was defined as Lichtiger response at days 5, 6, and 7, i.e. scores of <10 points with a decrease of ≥3 points compared with baseline scores). In addition, all patients with a clinical response were started or continued on azathioprine 2 to 2.5mg/kg/day. Patients continued to receive corticosteroid iv at a stable dose until day seven and this was switched in patients with a clinical response to oral methylprednisolone 30mg daily which was tapered with an aim to discontinue.

The primary endpoint, measured at day 98, was treatment failure at any time, defined as the presence during follow-up of any of the following six criteria: absence of clinical response at day 7; relapse between day 7 and 98 (defined as a ≥3-point increase in Lichtiger score increase from the previous value that lasts for at least three consecutive days and leads to treatment modification); absence of steroid free remission at day 98 (defined as a Mayo disease activity index score ≤2 with an endoscopic sub-score ≤1); severe adverse event leading to treatment interruption; colectomy or death. At day 98, treatment failure occurred in 60% (35/58) of ciclosporin patients compared with 54% (31/57) of infliximab patients; absolute risk difference 6%, 95% confidence interval (CI) -7% to 19%; OR 1.3, 95% CI 0.6 to 2.7; p=0.52.

Secondary endpoints included mucosal healing at day 98 (defined by a Mayo disease activity index endoscopic sub-score of 0 or 1) and was achieved in 47% (26/55) of patients in ciclosporin group versus 45% (25/45) of patients in the infliximab group; absolute risk difference 2%, 95% CI -17% to 20%; OR 1.1, 95% CI 0.5 to 2.3; p=0.85. There was a similar number of colectomies: 10 in the ciclosporin group (17%) and 12 in the infliximab group (21%). Quality-of-life changes from baseline to day 98 (measured with the inflammatory bowel disease questionnaire) were available in 19 patients in the ciclosporin group and 17 patients in the infliximab group. The median score increased from baseline to day 98 by 78 points (inter-quartile range [IQR] 66 to 104, n=19) versus 100 points (IQR 75 to 112, n=17) in the respective groups.

Two phase III randomised, double-blind, placebo-controlled studies of similar design (ACT 1 and ACT 2) were conducted in patients with moderate to severe active UC despite treatment with concurrent medications and a Mayo score of 6 to 12 points (range, 0 to 12; higher scores indicate more severe disease activity).[6] Concurrent treatment included corticosteroids alone or in combination with azathioprine or mercaptopurine (in ACT 1 and 2) and also medications containing 5-aminosalicylates in ACT 2. Patients were considered to have UC that was refractory to corticosteroids if symptoms had not improved after ≥40mg of oral prednisone daily (or equivalent) for ≥2 weeks or iv for ≥1 week. Patients were randomised equally to receive infliximab iv infusion 5mg/kg (licensed dose), infliximab 10mg/kg or placebo at weeks 0, 2, and 6 and then every eight weeks to week 46 in ACT 1 and week 22 in ACT 2. Patients were followed up to week 54 in ACT 1 and week 30 in ACT 2.

The primary endpoint was clinical response at week 8, defined as a decrease from baseline in the total Mayo score of ≥3 points and at least 30%, with an accompanying decrease in the sub-score for rectal bleeding of ≥1 point or an absolute sub-score for rectal bleeding of 0 or 1. A clinical response was achieved in significantly higher proportions of patients in the infliximab 5mg/kg and 10mg/kg groups than placebo group for both studies (p<0.001). Secondary endpoints included clinical remission (defined as a Mayo total score of ≤2 points, with no individual sub-score >1 point at week 8), mucosal healing (defined as an absolute sub-score for endoscopy of 0 or 1 at week 8) and sustained clinical response and remission (at weeks 8, 30 and 54 in ACT 1 and weeks 8 and 30 in ACT 2). For all secondary endpoints, infliximab 5mg/kg and 10mg/kg were significantly superior to placebo for ACT 1 and ACT 2. Results of the primary and secondary endpoints are included in the table below.

Table; results of primary and some secondary endpoints for ACT 1 and ACT 2 studies

	ACT 1			ACT 2		
	Infliximab 5mg/kg	**Infliximab 10mg/kg**	**Placebo**	**Infliximab 5mg/kg**	**Infliximab 10mg/kg**	**Placebo**
N	121	122	121	121	120	123
Primary endpoint						
Clinical response at week 8, n (%)	84 (69%)	75 (61%)	45 (37%)	78 (64%)	83 (69%)	36 (29%)
Secondary endpoints						
Clinical remission at week 8, n (%)	47 (39%)	39 (32%)*	18 (15%)	41 (34%)	33 (27%)	7 (5.7%)
Mucosal healing at week 8, n (%)	75 (62%)	72 (59%)	41 (34%)	73 (60%)	74 (62%)	38 (31%)

*p=0.002; p<0.001 for other comparisons of infliximab versus placebo

Sustained clinical responses and remissions were achieved in a significantly higher proportion of patients in the infliximab groups than placebo group for both studies. At week 54 there was a numerical difference for infliximab 5mg/kg and statistically significant difference for infliximab 10mg/kg compared to placebo for the proportion of patients requiring a colectomy (pooled results: infliximab 5mg/kg 12% [28/242] versus infliximab 10mg/kg 7.4% [18/242] versus placebo 15% [36/244]). There were no statistically significant differences between infliximab 5mg/kg and placebo in subgroup analyses of colectomy in patients with different disease severities.[7]

Summary of evidence on comparative safety

The safety profile of infliximab in the treatment of UC was considered similar to treatment of other approved indications, in particular Crohn's disease.[8] Refer to the summary of product characteristics for infliximab for full details of adverse events.[2]

Severe adverse events that occurred during the comparative study included cardiovascular events (one patient in ciclosporin group versus one patient in the infliximab group); severe infections (five versus four patients); hepatic events (none versus four patients with increased aminotransferases leading to treatment withdrawal [two cases linked with azathioprine]); pulmonary event (one patient with unconfirmed suspected pneumonia versus none); worsening of UC (three versus seven patients); and degenerative arthrosis (none versus one patient). The severe infections in the ciclosporin group included cytomegalovirus colitis (n=2), septicaemia (n=2) and fever of unknown origin (n=1). The severe infections in the infliximab group included cytomegalovirus colitis, urinary tract infection, anal abscess and fever of unknown origin (one patient each).

Summary of clinical effectiveness issues

The submitting company has requested that SMC considers infliximab when positioned for use as an alternative to ciclosporin in adult patients with acute, severe UC (i.e. in the context of 'rescue therapy' as opposed to the maintenance phase of treatment). There are limited treatment options for this clinical situation and clinical experts consulted by SMC considered this was an area of unmet need. UK and European guidance recommends off-label ciclosporin (iv followed by oral treatment) or infliximab in patients with acute severe UC who have little or no improvement within 72 hours of starting intravenous corticosteroids or whose symptoms worsen at any time despite corticosteroid treatment.[3,4,5] The National Institute for Heath and Care Excellence (NICE) guidance restricts infliximab to situations when ciclosporin is contraindicated or clinically inappropriate.[5] Infliximab is licensed for use in severely active UC in children and adolescents and SMC has accepted it for restricted use as an alternative to ciclosporin in patients with acute, severe paediatric ulcerative colitis (rescue therapy) who are steroid refractory.

Results of the primary and secondary endpoints in the open-label comparative study, in patients with active severe UC, were similar for ciclosporin and infliximab, with wide confidence intervals for treatment differences. However the study has some limitations. Firstly, the sample size of this superiority study was based on an assumption of 30% difference between treatments (reduced to 15% difference at interim analysis) which was not realised in practice. Furthermore, the study was not designed nor had a sufficient sample size for a non-inferiority analysis. Other limitations include use of the non-validated Lichtiger scale and the open-label design of the study (although this was difficult to avoid given the monitoring requirements for patients treated with ciclosporin). Overall, the comparative efficacy of ciclosporin versus infliximab is uncertain. There is a lack of other head-to-head studies versus ciclosporin for the positioning proposed by the submitting company.

The double-blind, placebo-controlled studies showed significant differences for infliximab versus placebo for endpoints measured at week eight and for sustained clinical response and remission measured at week 54 and week 30 for ACT 1 and ACT 2 respectively. However, patients were required to have moderate to severe active UC (Mayo score of 6 to 12), which is relevant to the licensed indication, but not the positioning where patients are to have acute severe UC. The mean Mayo score at baseline was approximately 8.4 compared to a Mayo score >10 for severe UC; no subgroup analyses in severe UC were included in the clinical sections of the company's submission or reported in the key publication. There was no significant difference between infliximab 5mg/kg and placebo at week 54 in terms of incidence of colectomy; however, the risk of colectomy was small in the overall patient population of moderate to severe UC. Also, as patients continued to receive infliximab every eight weeks, end-points after week 14 (including data from the extension studies) are relevant for assessment of efficacy in maintenance of remission rather than induction of remission. Finally, another limitation is lack of clarity in terms of how double-blindness was achieved.

The European Medicines Agency (EMA) did not consider the results of the placebo-controlled studies showed a favourable benefit risk balance for infliximab 10mg/kg dose regimen.[8] Consequently, the licensed dose of infliximab for UC is 5mg/kg.

Infliximab is a licensed alternative treatment for induction of remission of active, severe, UC in a defined patient group. Clinical experts considered infliximab to be a therapeutic advancement as it would provide a treatment choice other than off-label ciclosporin or colectomy in patients with severe UC. There may be advantages for the patient and service delivery in terms of administration of infliximab (given as three, 2-hour iv infusions) compared to ciclosporin which is given as a continuous iv infusion for seven days (followed by oral treatment) and requires careful monitoring. However, clinical experts views on whether the inpatient stay would be less with infliximab compared to ciclosporin treatment were mixed.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing infliximab with ciclosporin as rescue therapy in adult patients with acute, severe UC 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. The time horizon of the analysis was 54 weeks.

A Markov model was used which involved two treatment phases: rescue therapy (where patients received ciclosporin or infliximab) and maintenance therapy (where both arms received aminosalicylates). The model included three UC disease health states of remission, mild/moderate disease and severe disease. Surgery, with and without complications, was also included in the model.

The clinical data used in the infliximab arm of the model were taken from a subgroup of a pooled analysis of the ACT 1 and ACT 2 studies. The subgroup of patients used in the economic analysis included patients who had active severe disease at baseline (Mayo score of 11 or 12), were corticosteroid-refractory and received infliximab 5mg/kg. This resulted in a very small subgroup of only 5 patients. Transition probabilities used in the model were then derived from the pooled analysis of this subgroup of patients. For the ciclosporin arm of the model, transition probabilities were derived using the odds ratio of treatment failure from the comparative study described above (odds ratio 1.3). The difference in treatment failure was not statistically significant (p=0.52) but was used in the model.

Data on the quality of life of patients in each UC health state were taken from a study where quality of life was measured according to disease severity using the EQ-5D-5L questionnaire. For the utility values relating to patients receiving surgery, the company identified a published study which evaluated the quality of life of patients post-surgery using the time trade-off technique.

Costs included drug acquisition costs, administration costs, concomitant treatments and the cost of adverse events. Disease management costs (including hospitalisations, GP visits, outpatient visits and other monitoring costs) were included based on clinical expert opinion.

In the base case analysis, the submitting company estimated a cost per quality-adjusted life-year (QALY) of £21,615 based on an incremental cost of £186 and a QALY gain of 0.0086. One-way sensitivity analysis was performed to test the model parameters. The results were most sensitive to changes in the efficacy assumptions, hospitalisation costs and administration costs. Results were also moderately sensitive to changes in the utility values.

The following limitations were noted:

- The approach used to estimate the clinical data in the model has several limitations. Comparative study data are available comparing infliximab with ciclosporin, but the company argued it was not possible to use these data directly in the model as the available data only reported the proportion of patients who responded to treatment. The proportion of patients who achieved remission was not reported. Instead, the company took data from a very small subgroup of just five patients from the ACT 1 and ACT 2 placebo-controlled studies for the infliximab arm and then applied the odds ratio from the comparative study to estimate the transition probabilities for the ciclosporin arm.

- The model estimates that infliximab is the more effective treatment. However, the comparative study did not show a significant difference between the treatments. When infliximab and ciclosporin were assumed to have the same efficacy, ciclosporin became the dominant treatment (i.e. infliximab became more expensive but no more effective). A threshold analysis provided by the company indicated that the odds ratio only had to reduce slightly from 1.3 to

1.28 before the cost per QALY increased to £30k.

- The key issue with the resource use estimates was the assumption that the length of stay in hospital for patients treated with infliximab is less than patients treated with ciclosporin (7 days vs 10 days). This may not be appropriate, particularly given the lack of robust clinical data to demonstrate improved efficacy with infliximab. SMC clinical expert views on whether infliximab treatment would reduce inpatient stay were mixed. When length of stay was assumed to be 7 days in both arms, the cost per QALY increased to £147k.

- The time horizon used in the analysis may not be appropriate. The company selected the short time horizon based on the duration of the infliximab studies and the lack of long-term data. However, a longer time horizon may be more appropriate as patients who remain uncontrolled after treatment are assumed to receive surgery, which involves a large upfront cost but benefits would potentially accrue over a number of years. As more patients in the ciclosporin arm are assumed to require surgery, the shorter time horizon could bias the analysis in favour of infliximab.

Due to the weaknesses outlined above, the economic case has not been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Information Group.

- A submission has been received from Crohn's and Colitis UK, which is a registered charity.

- Crohn's and Colitis UK has received funding from several pharmaceutical companies in the last two years.

- Patients report that ulcerative colitis has a significant impact on their physical, emotional and psychological health. Unpredictable flare-ups can cause crippling pain and an urgency to use the toilet, fatigue, anaemia and rapid weight loss. Ulcerative colitis can impact on interpersonal relationships, self-esteem and the ability to work and study, especially as many patients are at a younger age. The potential impact of surgery on patients self confidence can also be significant.

- Crohn's and Colitis UK reports that infliximab has been seen to reduce the symptoms of severe, active ulcerative colitis and has enabled patients to participate in daily life once more. Infliximab may help bring a patient's condition into remission, potentially delaying or preventing the need for surgery in severe ulcerative colitis and potentially providing an improvement in patients' quality of life, enabling them to work, socialise and regain their self-esteem.

Additional information: guidelines and protocols

NICE issued clinical guideline 166; Ulcerative colitis: Management in adults, children and young people, in June 2013.[5] The guideline includes the following recommendations for treatment of acute severe UC:

Step 1

- For people admitted to hospital with acute severe ulcerative colitis (either a first presentation or an inflammatory exacerbation):
    - offer intravenous corticosteroids to induce remission and
    - assess the likelihood that the person will need surgery

- Consider intravenous ciclosporin or surgery for people:
    - who cannot tolerate or who decline intravenous corticosteroids or
    - for whom treatment with intravenous corticosteroids is contraindicated.

Take into account the person's preferences when choosing treatment.

Step 2

- Consider adding intravenous ciclosporin to intravenous corticosteroids or consider surgery for people:
    - who have little or no improvement within 72 hours of starting intravenous corticosteroids or
    - whose symptoms worsen at any time despite corticosteroid treatment.

Take into account the person's preferences when choosing treatment.

- For guidance on infliximab for treating acute severe ulcerative colitis (all extents of disease) in people for whom ciclosporin is contraindicated or clinically inappropriate, refer to Infliximab for acute exacerbations of ulcerative colitis (NICE technology appraisal guidance 163).

The British Society of Gastroenterologists published an update to the guideline for the management of inflammatory bowel disease in adults in 2010.[3] In patients with acute severe UC iv corticosteroids are used together with supportive treatments. If there is no improvement by day three or there is subsequent deterioration then rescue therapy should be administered; ciclosporin 2mg/kg/day (and then after remission induction ciclosporin orally for 3 to 6 months) or infliximab iv 5mg/kg on weeks 0, 2 and 6. The guidelines states that infliximab should not be used for maintenance. If no response to rescue therapy is seen within 4 to 7 days, colectomy is recommended; in this situation the use of infliximab following ciclosporin (and vice versa) is not recommended. Patients with UC should normally receive maintenance therapy with aminosalicylates, azathioprine, or mercaptopurine to reduce the risk of relapse.

The European Crohn's and Colitis Organisation published a guideline on the management of UC, in 2012.[4] In patients with acute severe UC conventional therapy is with iv corticosteroids. The response to iv steroids is best assessed objectively around day three. Treatment options including colectomy should be discussed with patients with severely active UC not responding to iv steroids. Second line therapy with either ciclosporin, or infliximab or tacrolimus may be appropriate. If there is no improvement within 4 to 7 days of salvage therapy, colectomy is recommended. Maintenance treatment is recommended for all patients and choice is determined by disease extent, disease course (frequency of flares), failure of previous maintenance treatment, severity of the most recent flare, treatment used for inducing remission during the most recent flare, safety of maintenance treatment, and cancer prevention.

Additional information: comparators

Ciclosporin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Infliximab	**5mg/kg iv on days 0, 14 and 42**	**5,035**
Ciclosporin	2mg/kg/day iv for seven days then 4mg/kg/day orally (as two divided doses) for 12 weeks.	464

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis and MIMS on 3 February 2014. Doses based on body weight of 70kg. Ciclosporin is not licensed for treatment of UC.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 661 in year 1 and 675 in year 5. The uptake rate was estimated to be 29% in year 1 (192 patients) and 41% (277 patients) in year 5.

The gross impact on the medicines budget impact was estimated to be £964k in year 1 and £1.39m in year 5. As other drugs were assumed to be displaced, the net budget impact was £909k in year 1 and £1.31m in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Laharie D, Bourreille A, Branche J,et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet. 2012; 380(9857): 1909-1915.

2. Merck, Sharp & Dohme Ltd. Summary of product characteristics for infliximab (Remicade®). Last updated June 2013.

3. Mowat C, Cole A, Windsor A, et al; IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2011; 60(5): 571-607.

4. Dignass A, et al, Second European evidence-based Consensus on the diagnosis and management of ulcerative colitis: Current management, Journal of Crohn's and Colitis (2012), http://dx.doi.org/10.1016/j.crohns.2012.09.002

5. NICE. Clinical guideline 166; Ulcerative colitis: Management in adults, children and young people. June 2013.

6. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis, N Engl J Med. 2005; 353; 2462-2476.

7. European Medicines Agency. Assessment report for infliximab (Remicade). EMEA/H/C/II/107. 21 February 2007

8. European Medicines Agency. Assessment report for infliximab (Remicade). EMEA/H/C/240/II/65. 26 January 2006

This assessment is based on data submitted by the applicant company up to and including 14 March 2014.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.