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UK Medicines Information Pharmacists Group

NEW MEDICINES ON THE MARKET

Evaluated information for the NHS

Infliximab in the treatment of Crohn's disease

Summary

- Infliximab, a chimeric monoclonal antibody with a high specificity and affinity for tumour necrosis factor (TNF α), is licensed for severe, active Crohn's disease and fistulising Crohn's disease, refractory to other drugs.
- Limited trial evidence has shown that infliximab, in the currently licensed dose of 5mg/kg, produces a significant and rapid clinical response in refractory Crohn's disease, improvement in endoscopic, histological and biochemical indices of response and healing of fistulae. Since available trials are dose ranging, further trials of infliximab at the licensed dose are desirable.
- While the adverse effects of infliximab are claimed to be predominantly mild to moderate in severity, an association between use of infliximab and the development of lymphoma is suggested by several case reports. Whether these reflect a link between inflammatory bowel disease and lymphoma or an increased risk with the use of infliximab is unknown.
- Infliximab is contraindicated in patients with severe infections such as sepsis, abscesses or tuberculosis. Its effects on immune response may predispose patients to opportunistic infections; cases of tuberculosis have occurred during its use. Careful monitoring of patients for infections, both during and after cessation of treatment is essential.
- Moderate to severe hypersensitivity reactions, which can occur on subsequent drug use, have been reported. Readministration of infliximab after a drug free interval of 15 weeks, cannot be recommended. The availability of appropriate resuscitation facilities is essential when infliximab is administered.
- Infliximab is an extremely expensive drug, a consideration which imposes the need for use of strictly defined patient selection policies. Cost and safety issues dictate that it must be used under the supervision of specialised physicians experienced in the diagnosis and treatment of inflammatory bowel disease.

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Infliximab for Crohn's disease

APPROVED NAME:	Infliximab
BRAND NAME (MANUFACTURER):	Remicade (Marketing Authorisation Holder - Centocor BV/ Marketed by Schering Plough)
PRESENTATION:	Each vial of Remicade contains 100mg of infliximab and excipients. Upon reconstitution with the recommended volume of water for injections (see SPC for details) each ml contains 10mg of infliximab.
BNF THERAPEUTIC CLASS:	Inflammatory bowel disease - 1.5.
LICENSED INDICATIONS:	<ol style="list-style-type: none">1. Treatment of severe active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant.2. Treatment of fistulising Crohn's disease in patients who have not responded despite a full and adequate course of therapy with conventional treatment
DOSAGE AND ADMINISTRATION:	See SPC for precautions in administration. Remicade treatment is to be administered under the supervision of specialised physicians. Severe, active Crohn's disease – 5mg/kg as an intravenous infusion over a 2-hour period. Fistulising Crohn's disease - An initial 5mg/kg infusion over a 2-hour period is to be followed with additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion. Re-administration after a drug-free interval of 15 weeks is not recommended. The use of infliximab in children (0-17 years) has not been studied.
THERAPEUTIC COMMENT:	Limited trial evidence supports use of infliximab in the treatment of severe Crohn's disease refractory to conventional treatments. Its inhibitory effects on immune response may lead to the development of opportunistic infections (including tuberculosis) and an unproven association with lymphoma has been mooted. These considerations, together with its high costs, require that it be used under the direct supervision of specialists concerned with the treatment of inflammatory bowel disease. Close postmarketing surveillance, together with detailed recording of clinical experience with its use, are advisable.
SECTOR OF USE:	Hospital [Y] Primary Care [N]
COST AND COURSE DETAILS:	Single dose treatment (350mg) for 70kg patient – 350mg – £1579.20
TREATMENT ALTERNATIVES:	No other monoclonal antibodies are licensed for use in Crohn's disease. Since infliximab is indicated for disease which is refractory to conventional treatments, price comparisons with such treatments are inappropriate.

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INTRODUCTION

Crohn's disease is a chronic inflammatory bowel disorder characterised by segmental transmural inflammation and granulomatous changes. Although any part of the gut may be affected, the distal small intestine and colon are primary targets. Incidence varies according to ethnicity, but is distributed evenly between the sexes with a peaking in occurrence between the ages of 15 and 35 years. Major symptoms include diarrhoea, abdominal pain, fever and fatigue, sometimes accompanied by anorectal abscesses, fissures and fistulae. Serious complications include small bowel or colonic malignancies [1]. It is estimated that there are between 30,000 and 40,000 patients with Crohn's disease in the UK. Approximately 25% may have severe disease, of whom a small proportion are unresponsive to current treatments [2].

The aetiology of Crohn's disease remains unknown and treatment has traditionally focussed on the use of anti-inflammatory drugs, corticosteroids, antibiotics and immunosuppressive agents. The introduction of infliximab, a TNF α (tumour necrosis factor alpha) inhibitor for Crohn's disease refractory to such treatments, provides a novel anti-inflammatory approach.

PHARMACOLOGY

TNF α is a pro-inflammatory and immunoregulatory cytokine that mediates diverse effects, including chronic inflammation, in organs and tissues. It is thought to play an important role in the aetiology of Crohn's disease, its levels being raised in all types of cells, tissues and secretory fluids of patients with this disorder [3]. In the past few years, several compounds have been developed which neutralise or impair the production of TNF α including oxpentifylline, p65 antisense oligonucleotides and metalloproteinase inhibitors [3].

Infliximab is a chimeric (i.e. derived from two distinct species) human-murine monoclonal antibody. It binds with high affinity and specificity to human TNF α , inhibiting its functional activity (as demonstrated in a variety of *in vitro* bioassays) and neutralising soluble TNF α and membrane-bound TNF α precursors [1].

PHARMACOKINETICS

At the recommended single dose of 5mg/kg infliximab, the median C_{max} value was 118 micrograms/ml. Following doses of 3, 5 or 10mg/kg, median half-lives ranged from 8 to 9.5 days. In most patients given 5mg/kg, infliximab could be detected in the serum for a period of at least eight weeks. Repeated administration at two and six weeks resulted in slight accumulation [4].

The pharmacokinetics of infliximab in elderly patients, or in those with liver or renal disease, have not been studied. Corticosteroids do not appear to affect the pharmacokinetics of infliximab to a clinically relevant extent. Nothing is known concerning interactions with other drugs [4].

EFFICACY

Evidence for the clinical efficacy of infliximab rests on the outcome of a small number of randomised, controlled trials (some using the same trial population) and various uncontrolled trials, often with low subject numbers. The essential features of these trials are summarised in the table. The majority of trials are dose-ranging. Consequently, only sub-groups of patients were allocated the licensed dose of 5mg/kg. This clearly hinders extrapolation to routine clinical usage. Among the randomised controlled trials, only one provides a power estimate [5].

The trials utilise a number of response indices. Such indices include the Crohn's Disease Activity Index (CDAI), which measures both clinical response and

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laboratory findings, Inflammatory Bowel Disease Questionnaire Scores (a quality of life assessment), serum C-reactive protein levels, endoscopic assessment as measured by the Crohn's Disease Endoscopic Index of Severity (CDEIS) and histological findings from gut biopsy specimens.

A criticism of the trials is that the entry criteria may not invariably match the licensed indications for infliximab i.e. severe disease exacerbation with documented resistance to conventional treatments [6]. The clinical significance of a reduction of 70 points in the CDAI score, used as a primary outcome measure in most trials, has also been questioned; such a reduction may not bring patients into a range reflecting remission [7]. Furthermore, methods of reporting CDAI are statistically inconsistent, variously utilising means with standard errors [8], with standard deviations [5] or, more appropriately, medians with interquartile range [9].

A pivotal study of infliximab in Crohn's Disease is that of Targan *et al.* [5]. Clinical response was achieved early, and at two weeks 61% of patients given infliximab had a clinical response compared with only 17% in the placebo group ($p < 0.001$). An extension arm of this trial showed that failure to respond to an initial dose of infliximab was associated with a lack of response to further infliximab treatment. Although adverse effects occurred with similar frequency in all arms of the trial, chest pain, dyspnoea and nausea occurred in two patients receiving infliximab and resolved on discontinuation of infusion; two others required hospital admission (for abdominal abscess and salmonella colitis, respectively). Examination of serum samples at 12 weeks for the presence of antibodies to infliximab proved inconclusive, possibly because infliximab was still detectable.

In a further extension of the Targan study, Rutgeerts *et al.* [10] showed that repeated dosing with infliximab to initial responders maintained clinical

response and remission for up to 44 weeks, although treatment benefit achieved only "borderline" significance (possibly through lack of power). The choice of a 10mg/kg dose for repeated treatment, rather than the 5mg/kg dose shown to be optimum in the initial trial, is not explained. In this study, one case of lymphoma and one of suspected lupus were observed, leading the authors to advise that the safety profile of infliximab requires additional clinical investigation.

D'Haens *et al.* [8] reported on a subgroup of patients from the Targan study who underwent ileocolonoscopy before and after treatment, to examine the relationship between clinical response and reduction in mucosal inflammation. Significant endoscopic improvement was observed in infliximab-treated patients with a drop in mean CDEIS scores from 15.1 to 6.4 for the 5mg/kg group ($p = 0.006$), from 10.6 to 4.3 in the 10mg/kg group ($p = 0.009$), and from 13.3 to 5.2 in the 20mg/kg group ($p = 0.006$). No endoscopic improvement was observed in the placebo group, however, this group had a lower baseline score (8.4 to 7.5). Standard errors for all values were large, doubtless reflecting low sample numbers and wide intersubject variation and suggesting that median scores would have been more informative. The authors observed that changes in endoscopic scoring correlated with CDAI scoring ($r = 0.56$, $p = 0.002$).

The trial reported by Present *et al.* [9] focussed specifically on healing of fistulae, utilising the Perianal Disease Activity Index (PDAI) as a measure of response. A marked healing of fistulae with infliximab was observed but more than 60% of patients in all groups (including placebo) experienced adverse effects. Three of 92 patients showed antibodies to infliximab. However, none of the adverse reactions observed in these patients were suggestive of a sensitivity reaction.

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On the basis of available data, the duration of effect of a single 5mg/kg dose of infliximab appears to be between 8 and 12 weeks [11].

In a recent published review [7], infliximab is considered to offer "the potential to radically alter the course of severe cases of Crohn's disease". While accepting anti-TNF α treatment as a therapeutic option, it is argued that trials are needed to compare it with other options and with newer (currently unlicensed) immunosuppressants such as tacrolimus and thalidomide. Infliximab has a role, it is suggested, for the ill patient in whom an effective treatment is urgently required while immunosuppression with azathioprine, which can take up to six months, is being established.

An international working group [12] has also published recommendations regarding the use of infliximab. They state that it should not be regarded as a first-line treatment but should be used in active phase recurrent disease (including fistulising disease) if standard treatment proves unsuccessful. These recommendations are consistent with current licensed indications.

PROMOTIONAL DATA

A promotional brochure for infliximab bearing the legend "Welcome to the future... Remicade ...in the treatment of Crohn' disease" shows a representation of the infliximab molecule in an astronomical setting, implying, presumably, that the introduction of this drug may herald significant future developments in the management of Crohn's disease. Claims for healing, quality of life and remission appear compatible with available trial evidence. Use of the greek character α in the spelling of Remicade provides a subtle link with the mode of action of this drug.

ADVERSE EFFECTS

Adverse effects with infliximab are reported to be mild

to moderate in severity (although moderate to severe hypersensitivity effects have been reported). Symptoms affecting the skin, respiratory system and appendages have been reported most frequently. Effects that most usually prompt discontinuation of treatment are dyspnoea, urticaria and headache. Common reactions (occurring with a frequency of $> 1/100$) have included viral infection, vertigo, flushing, respiratory infections, gastrointestinal disturbances, abnormal hepatic function, fatigue and chest pain.

A possible association between use of infliximab and the development of lymphoma has been discussed in several reports [13]. This must be judged against evidence of a possible association between lymphoma and Crohn's disease [14]. The incidence of lymphoma and other malignancies in patients given infliximab is reported to be similar to that expected for the populations studied [4].

Opportunistic infections have been reported in patients treated with infliximab, suggesting that that host defence mechanisms are compromised. Warnings have recently been issued concerning the occurrence of active tuberculosis in patients treated with infliximab [15] leading to part revision of the SPC.

CONTRAINDICATIONS AND PRECAUTIONS

Readministration of infliximab with a drug free interval of 2 to 4 years following a previous infusion has been associated with delayed hypersensitivity reactions including myalgia and/or arthralgia, fever and rash in a significant proportion of patients. The risk of delayed hypersensitivity after a drug-free interval of 15 weeks to 2 years is unknown and the SPC recommends against readministration of infliximab after a drug free interval of 15 weeks. However, recent evidence has suggested a lack of delayed hypersensitivity reactions on readministration following intervals of up to 6 months [20].

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Antibodies to infliximab develop in some patients and may rarely cause serious allergic reactions. Patients who are intolerant of non-corticosteroid immunosuppressants and discontinue these prior to or during infliximab treatment are potentially at greater risk of developing these antibodies, which cannot always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and infliximab discontinued.

Infliximab is contraindicated in patients with severe infections such as sepsis, abscesses and tuberculosis. Patients must be monitored closely while on, and after, treatment; because the elimination of infliximab may take up to six months, monitoring patients throughout this period is important.

Initiation of an autoimmune process may occur in a subgroup of genetically susceptible patients. Infliximab should, therefore, be discontinued if the patient develops lupus like symptoms.

There are insufficient data to draw conclusions on the possible effects of infliximab on fertility. Use in pregnancy is not recommended since immune responses in the newborn could be adversely affected. Women should not breast feed for at least 6 months after infliximab treatment.

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Randomised controlled trials of infliximab in Crohn's disease									
Ref No	Design of Study	Primary Outcome Measures	Treatments Assessed	Results and Comments					
5	Multicentre 12 week study in patients with moderate to severe Crohn's disease (CDAI scores 220 - 400). Extension study - open label subgroup of patients unresponsive to initial dose (19 placebo/29 infliximab)	Clinical response - defined as reduction of 70 or more points in CDAI score. Clinical remission - CDAI score <150. IBDQ C-reactive protein serum concentrations.	Single doses of infliximab: 5mg/kg (n=27) 10mg/kg (n=28) 20mg/kg (n=28) placebo (n=25)	Clinical Response		Overall remission rate		Increase in IBDQ score	C-reactive protein
				4 weeks	12 weeks	4 weeks	12 weeks	4 weeks	4 weeks
				81%	48%	33% (all doses)	24% (all doses)	36	-14.3mg/l
				50%	29%				
				64%	46%				
				17%	12%	4%	8%	5	+2.0mg/l
			p (aggregate) <0.001	p (aggregate) =0.008	p=0.005	p=0.31	p=0.001	p<0.001	
			Extension study All patients given infliximab 10mg/kg	Extension study			Clinical response/4 wk	Clinical remission/ 4 wk	
				Pt unresponsive to initial dose of infliximab			34%	17%	
				Pt unresponsive to initial dose of placebo			58%	47%	
10	Multicentre extension of above study in pt with initial clinical response to infliximab (n=37) or placebo (n=36)	As above	Treatment given 4 times every 8 weeks Infliximab 10mg/kg Placebo	Clinical response until wk 44		Clinical remission until wk 44		Dropouts	
				62%		53%		10	
				37% (p=0.16)		20% (p=0.013)		14	
Open label studies of infliximab in Crohn's disease									
16	7 pt with Crohn's disease of the ileoanal pouch	Categorical assessment – complete/partial/no response	Infliximab 5mg/kg 1-4 doses	6 pt had a complete response 1 pt had a partial response					
17	10 pt with active inflammation	CDAI scores and colonoscopy	Infliximab 10mg/kg (n=8) or 20mg/kg (n=2)	8 showed normalisation of CDAI scores with near complete healing of ulceration within 4 weeks of treatment. Relapse occurred within 3 to 6 months.					
18	12 pt with severe disease	CDAI scores and endoscopic evaluation	Infliximab 0.5mg/kg as initial dose then 0.5mg or 1mg/kg daily for 6 days	2 pt had prolonged, and 2 pt partial improvement. Significant endoscopic improvement seen in only 1 pt.					
19	20 pt with active disease	CDAI scores and endoscopic evaluation	Infliximab in doses of 1, 5, 10 or 20mg/kg	Clinical response (reduction in CDAI score ≥70) at 12 weeks: 1mg/kg 20%; higher doses 50-80% Substantial reduction in endoscopic lesion scores at 8 wks with 3 higher doses.					
Randomised controlled trial of infliximab in fistulising Crohn's disease									
9	Pt with draining abdominal or perianal fistulae of at least 3 months duration. Follow up – 34 weeks	Primary: reduction of at least 50% from baseline in number of draining fistulae observed at 2 or more consecutive visits. Secondary: closure of all fistulae	3 doses (at 0, 2 + 6 weeks) Infliximab 5mg/kg (n=31) 10mg/kg (n=31) Placebo (n=31)	Primary response		Secondary response		Median duration of fistulae closure 3 months	
				68% (p=0.002)		55% (p=0.001)			
				56% (p=0.02)		38% (p=0.04)			
				26%		13%			