Infliximab treatment for Crohn's disease

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Background

Crohn's disease is a lifelong inflammatory disorder characterised by the presence of inflammatory ulcerative lesions in the gastrointestinal tract.¹ Lesions most commonly involve the large and small bowel, giving rise to symptoms of abdominal pain, weight loss, gastrointestinal haemorrhage, and fistula formation.² The disease may present at any age, however the second and third decades of life represent the peak ages of diagnosis.³ Although the pathophysiology of Crohn's disease is unknown, a number of possible aetiologies have been reported. These include the interaction of environmental,⁴⁻⁵ infectious,⁶⁻⁸ genetic,⁹⁻¹⁰ or immunological¹³ factors. To date, treatment has been geared towards symptomatic relief of disease exacerbations via pharmacological interventions such as aminosalicylates, corticosteroids, immunosuppressive agents, antibiotics, and nutritional therapy. Surgery is indicated in those patients who have failed to respond to medical management, or to correct intestinal obstruction or abscesses. This can be up to 50% of sufferers.¹ Surgical intervention is by no means curative, with inflammatory episodes recurring in $\geq 80\%$ of patients after intestinal resection.¹¹

The advent of a therapy that can potentially restore immunological imbalance, modify the disease, and prolong remission in Crohn's disease patients, has thus been eagerly awaited.

Cytokine targeted treatment

The inflammatory response in Crohn's disease is regulated by intercellular mediators known as cytokines.¹² The major contributing factor to chronic local inflammation in Crohn's disease is local mucosal overproduction of proinflammatory cytokines to anti-inflammatory cytokines.¹³ Tumour necrosis factor- α (TNF- α) is one of several proinflammatory mediators, which has a central role in chronic inflammatory conditions, such as Crohn's disease, rheumatoid arthritis, and other granulomatous diseases. There are currently two anti-TNF antibodies under clinical evaluation, infliximab and CDP571.¹⁴ Infliximab (Remicade, Schering Plough, UK) is a chimeric monoclonal antibody to TNF- α , developed as a therapeutic agent for TNF- α mediated diseases. Infliximab acts by binding and neutralising TNF, high levels of which are found in the mucosa of Crohn's disease sufferers, and thus rendering it biologically inactive.¹⁵

Following approval the Food and Drug Administration in 1998, a number of international working group recommendations were published limiting its administration (box 1).¹⁶

In 1999, infliximab became available on the UK market for treatment of severe active or fistulising Crohn's disease, where patients had

inadequate response to conventional treatments. Although more expensive than current Crohn's disease treatment regimens, it has been suggested that fewer hospitalisations and surgical procedures (which account for 80% of Crohn's disease resource use and care expenditure), may result from infliximab infusion, and hence potentially induce cost savings to health-care systems. The latter is, however, wholly dependent on the annual number of infusions each patient requires when/if a patient relapses. Hay and Hay demonstrated that if a new treatment modality was developed that doubled drug costs, but led to a 20% reduction in medical costs, the annual expenditure associated with Crohn's disease would decrease by 13%.¹⁷ Although in the USA it remains to be established whether infliximab treatment results in a 20% reduction in medical costs, the savings incurred are moving in a positive direction.¹⁸

The recommended dose is 5 mg/kg body weight, but currently no standard guidelines exist as to the number of repeat infliximab administrations, or dosing interval between infusions, if relapse occurs. In the treatment of fistulae, however, repeat infusions are indicated if required, every 14 weeks. Work by Present and colleagues forms the clinical basis of working group recommendations of a total of three infusions in fistulising Crohn's disease.¹⁹

Clinical studies

The effect of infliximab on Crohn's disease management requires consideration of not only the acquisition cost, but also its impact on clinical outcome measures and safety. To date, 771 patients have received therapy with infliximab in clinical trials for the treatment of Crohn's disease, rheumatoid arthritis, or HIV infection (Schering-Plough Ltd, UK, personal correspondence, August 2000).

A summary of the pivotal studies in Crohn's disease patients is documented in table 1.

HISTOLOGICAL RESPONSE

The effect of infliximab on histological abnormalities has been investigated in two studies (table 1).²⁰⁻²¹ Both trials concluded that infliximab induced profound down-regulation of the inflammatory mechanisms in the entire mucosal layer. Four weeks after infusion there were reductions in the Crohn's disease activity index (CDAI; this is discussed later) and Crohn's disease endoscopic index of severity scores, together with a decline in C reactive protein concentrations.²¹ Although both trials document a virtual disappearance of neutrophils, a conflict in findings with regards to infliximab's effect on mucosal architecture is evident in these studies. In the earlier of the two trials, the mucosal architecture returned to normal in four patients,²⁰ whereas no patient in

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Box 1: Infliximab in Crohn's disease: recommendations of an international working group¹⁶

- **Active disease:** Steroids and immunosuppressants should not be eliminated as first line drugs in active Crohn's disease.
- **Recurrent disease:** In recurrent responsive disease, patients should receive steroid monotherapy or combined treatment with azathioprine. Infliximab should be reserved for patients if (1) steroids are contraindicated or (2) remission is not achieved within four months of combined treatment.
- **Chronic active disease:** In steroid dependent chronic active disease, azathioprine, and/or methotrexate are recommended as first line treatment(s).
- **Fistulae:** Infliximab is indicated if surgery, azathioprine, and/or antibiotic treatment are unsuccessful in fistulising disease.

the trial by D'Haens and coworkers obtained normal mucosal architecture, four weeks after infusion. Larger anti-TNF- α trials, which examine not only the histological and endoscopic response, but also the effect of repeat infusion on these outcomes, could prove useful in defining the antibody's precise mode of action.

FISTULA CLOSURE

The literature currently available documents no evident correlation between side effects and

Table 2 Percentage of patients reaching primary and secondary endpoints after treatment with infliximab or placebo¹⁹

	Placebo	Infliximab	
		5 mg/kg	10 mg/kg
Primary endpoint	26	68	56
p Value	—	0.002	0.02
Secondary endpoint	13	55	38
p Value	—	0.001	0.04

Primary endpoint: defined as $\geq 50\%$ reduction in the number of draining fistulae from baseline observed on at least two consecutive visits (21 days apart).

Secondary endpoint: defined as closure of all fistulae on at least two consecutive visits (21 days apart).

repeat infusion, and that no dose response exists. The largest of the published findings conducted in patients with draining abdominal or perianal fistulae of at least three months' duration, clearly demonstrates this.¹⁹ Present and colleagues defined the primary endpoint in their study as at least a 50% reduction in the number of draining fistulae from baseline observed on at least two consecutive visits (21 days apart). Closure of all fistulae on at least two consecutive visits represented the secondary endpoint. The favourable clinical responses associated with the lower dose of infliximab are significant (table 2), particularly when one considers that anal complications such as fissures, fistula or abscess formation develop in 15% of patients with Crohn's disease within five years of diagnosis.²²

The population recruited for this particular study included patients who had been receiving, and were maintained on, stable doses of immunosuppressants such as azathioprine/mercaptopurine (40%), corticosteroids (35%), and aminosaliclates (55%).¹⁹ Although the

Table 1 Key findings of clinical studies involving the treatment of Crohn's disease (CD) with infliximab

Reference	Design	Patient population	Acceptable concurrent trial medication	Findings
Targan <i>et al</i> , 1997 ²⁹	Multicentre, placebo controlled, double blind, randomised Infliximab 5 mg/kg (n=27)	Moderate-severe CD, with a CDAI score between 220–400	Stabilised doses of mesalamine; oral corticosteroids; 6-mercaptopurine; azathioprine	CDAI ≥ 70 point reduction occurred in 81% (n=22) of patients with moderate-severe disease patients, versus 17% in the placebo group (n=14). Remission at week 4 was evident in 48% of study patients compared to 4% in the placebo group
Rutgeerts <i>et al</i> , 1999 ²⁸	Placebo controlled, double blind, randomised Infliximab 10 mg/kg (n=37, 4 infusions 2 months apart)	Retreatment of patients ²⁹ with moderate-severe CD, with a CDAI score between 220–400	Stabilised doses of mesalamine; oral corticosteroids; 6-mercaptopurine; azathioprine	Infliximab gave a clinical response of 62% and remission of 52.9%, 8 weeks after the last infusion (week 44). This compares with a clinical response of 37% and remission of 20% at week 44 in the placebo group (n=36)
Baert <i>et al</i> , 1997 ²⁰	Multicentre, placebo controlled, double blind, randomised Infliximab 5 mg/kg (n=2), 10 mg/kg (n=7), 20 mg/kg (n=4) (as a single infusion), or placebo (n=5)	Crohn's ileocolitis	Stabilised doses of sulfasalazine/mesalamine; corticosteroids; antibiotics; azathioprine	Four weeks after infliximab resulted in a decrease in the total histological activity score (n=13), compared with the placebo group (n=5). In addition to the reduction in histological disease activity, the mucosal architecture of four patients returned to normal 1 month after infusion
D'Haens <i>et al</i> , 1999 ²¹	Multicentre, placebo controlled, double blind, randomised Infliximab 5 mg/kg (n=7), 10 mg/kg (n=7), 20 mg/kg (n=8) (as a single infusion), or placebo (n=8)	Active CD with a CDAI score between 220–400	Corticosteroids; azathioprine	Although inflammatory infiltrate disappeared in the treatment group after 4 weeks, the architectural abnormalities remained unchanged
Present <i>et al</i> , 1999 ¹⁹	Multicentre, placebo controlled, double blind, randomised Infliximab 5 mg/kg (n=31), 10 mg/kg (n=32) (at 0, 2, and 6 weeks), or placebo (n=31)	Draining abdominal or perianal fistulae of at least 3 months' duration	Stabilised doses of aminosaliclates; corticosteroids; 6-mercaptopurine; azathioprine	Fistula closure was obtained in 13% of the placebo population, 55% of those receiving 5 mg/kg infliximab, and 38% of those receiving 10 mg/kg infliximab The median duration of fistula closure was 3 months in the treatment groups

CDAI : Crohn's disease activity index.

overall response to infliximab infusion was independent of current treatment with these agents, subgroup analysis demonstrated that patients receiving immunosuppressants did not obtain a significant benefit with active therapy compared with placebo (59% *v* 44%, respectively; $p=0.46$).²³ This would suggest that subgroup analysis of response to treatment is an important design feature to be considered in future trials.

UNCONTROLLED STUDIES

In an "audit" of the medical notes of seven patients (five females, two males) with medically refractory Crohn's disease (after ileal pouch anal anastomosis), clinical response was reported as complete in six patients, and partial in one patient.²⁴ The trial participants received between one and four infliximab infusions at a dose of 5 mg/kg. No relapses occurred in the six patients after a median observation period of 13.4 weeks. Complete response was defined as cessation of fistulae, drainage and total closure of all fistulae, or cessation of diarrhoea, incontinence, and abdominal pain. Partial response was defined as either a decrease in the number, size, drainage, or discomfort associated with fistulae, or a reduction in diarrhoea and abdominal pain. Although these case reports document the efficacy of infliximab in a different patient population, the lack of scientific rigour of this publication places minimal weight on the conclusions drawn. This is highlighted particularly when the dosing schedule is examined—that is, variable dosing interval between infusions, together with inconsistency in the number of infusions administered.

ASSESSING CLINICAL RESPONSE

A crucial aspect of evaluating the efficacy of any new treatment modality is the choice of outcome measure. All but one study²⁴ discussed so far include the CDAI as a quantitative means of assessing patient progress or decline. The CDAI is a validated and widely used scale (score values 0–600) which dictates disease remission at scores <150, or severe disease activity at values >450.²⁵ The CDAI incorporates eight related variables: the number of liquid/very soft stools per day; the severity of abdominal pain/cramping; general wellbeing; the presence or absence of extraintestinal manifestations of disease; the presence or absence of an abdominal mass; the use of antidiarrhoeal drugs; the packed cell volume, and body weight. Regulatory authorities recognise the CDAI as the "gold standard" for assessing pharmacological efficacy in Crohn's disease clinical studies.²⁶ In addition, gastroenterologists in a large European study have reported its excellent correlation with clinical disease severity, when compared to another index.²⁷

Laboratory tests, endoscopic biopsies, and quality of life measures represent additional means of confirming Crohn's disease activity. The test results obtained from these assessments are often used as secondary outcome markers, in adjunct to the CDAI.

Clinical safety

Of the 199 patients with Crohn's disease treated with infliximab in clinical studies (average follow up of 27 weeks), the most common adverse effects reported were headaches (23% *v* 21% with placebo), upper respiratory tract infection (16% *v* 9% with placebo), and nausea (17% *v* 4% with placebo).

LYMPHOPROLIFERATIVE EFFECTS?

In the retreatment of 37 patients with four additional doses of infliximab (10 mg/kg), one 61 year old man developed an intravascular duodenal B-cell lymphoma, 9.5 months after this infusion.²⁸ Although this patient was in the placebo arm of this trial, he had been previously treated with a single infusion of infliximab in the initial part of the trial (10 mg/kg).²⁹ It is worth noting, however, that the patient had lymphopenia at baseline, and was receiving immunosuppressive therapy before infliximab administration.

Over 50 000 Crohn's disease patients have received multiple or single infusions of infliximab, and there have been two cases of lymphoma reported in this particular patient population. It remains unclear whether the existence of Crohn's disease itself puts patients at risk for developing lymphoma, since observational studies have led to conflicting results.^{30–33} Two factors which would suggest an increased risk, include:

- Existence of a chronically activated and abnormal immune system.³⁴
- Exposure to immunosuppressive therapies³⁵ and ionising radiation.³⁴

Although the precise mechanism of infliximab therapy in Crohn's disease is not fully understood, the absence of associations with reduced absolute lymphocyte count,³⁶ anergy development,³⁷ or opportunistic viral and fungal infections,³⁸ would suggest that TNF blockade with infliximab may lead to limited and selective immunosuppression, as opposed to broad spectrum immunosuppression.³⁴ Nevertheless, since the safety of infliximab beyond its recommended duration of treatment remains to be established, tumour surveillance via physical examination is advisable at each visit after infusion. The international working group also proposes that abdominal ultrasound and chest radiography is performed on an annual basis to detect for the development of lymphoproliferative disorders.¹⁶

Hypersensitivity reactions, differing in time of onset have also been observed. The majority of patients experienced reactions during or within two hours of infusion, although a small number of cases were documented 3–12 days after infusion.

In addition, treatment with infliximab has led to antinuclear and anti-dsDNA antibody development in 34% and 9% of patients respectively, between screening and last study visit. Baseline therapy with an immunosuppressant was, however, associated with reduced anti-dsDNA antibody development. Development of anti-dsDNA antibodies had no relation with dose or duration of infliximab. In one

patient, clinical signs consistent with a lupus-like syndrome were reported among infliximab treated trial participants. Improvement in symptoms was achieved by discontinuation of treatment and appropriate intervention (personal communication, Schering-Plough, UK).

It is worth noting that post-marketing adverse event data since product approval have been similar in type and occurrence in trial populations.

Cost of prescribing

In the UK alone, there are an estimated 30 000 Crohn's disease sufferers, 4.7% of whom have severe active disease, and a further 2.3% who have developed fistulae.³⁸ The actual cost of infliximab treatment is solely dependent on body weight and disease status—severe active requiring a single 5 mg/kg infusion, and fistulising patients requiring three such infusions at weeks 0, 2, and 6. It can hence be estimated that the cost of treating this target population with infliximab will be in the region of £1.575 million, in the UK alone (cost of treatment is based on an average weight of 75 kg). Since support groups for Crohn's disease sufferers, as with other patient groups, continue to apply pressure to healthcare teams for the introduction of new therapies among patients, it may be inevitable that this figure is an underestimation.

Promising anti-TNF alternatives

Although anti-TNF therapy has been cited to revolutionise the management of Crohn's disease, the current cost conscious healthcare environment will require the evaluation of alternative TNF inhibitors that prove to be less expensive without compromising clinical efficacy.

CDP571 (Celltech, Chiroscience, UK), which has a similar action to infliximab, is the second anti-TNF antibody to be clinically evaluated. Initial results in patients with moderate to severe Crohn's disease suggest a clinical effect beyond its half life.³⁹

The TNF receptor/Fc fusion protein etanercept (Enbrel, Immunex, USA) has provided excellent clinical response in patients with rheumatoid arthritis.⁴⁰ Preliminary investigations of its impact in Crohn's disease sufferers are underway. Thalidomide, which acts as an inhibitor in TNF production, has been assessed in a number of open label trials.^{41–42} In 14 patients with a CDAI score >200 and/or draining perianal disease who completed 12 weeks of treatment with 200 mg or 300 mg thalidomide, clinical remission was achieved in nine.⁴¹ Lower doses were reported to be effective in a pilot study of 12 males with moderate-severe, steroid dependent Crohn's disease. Disease activity improved consistently during the first month of thalidomide treatment. When steroid doses were reduced at week 5, clinical improvement was maintained up until trial completion (week 12).⁴³

Conclusion

Through a greater understanding of the pathogenesis of Crohn's disease, anti-TNF- α

antibody development has expanded the treatment options available for this debilitating condition. Although we are certain that good response is achieved in certain patient populations, the current published clinical data are incomplete. Establishing the long term efficacy and safety of infliximab, in addition to certain cost effectiveness issues, will become focal in future research. Firm guidelines relating to the use of infliximab in practice need to be established via outcome research. Infliximab administration is recommended in patients with fistulising or active Crohn's disease (defined as a CDAI score between 220–400), who have responded inadequately to conventional treatments. Extending its use outside this patient population should be prevented until good quality clinical studies dictate otherwise. The financial consequences of product use are dependent on the rate of relapse. The identification of an agent which could lengthen remission would be useful, hence reducing the requirement for repeat infliximab infusion in fistulising sufferers. Steroid sparing immunosuppressants such as azathioprine and 6-mercaptopurine represent investigative possibilities. The fact that the use of all immunosuppressants at baseline not only delays autoimmune response but also reduces infusion reactions, would suggest concurrent therapy to be beneficial. Coprescribing would, however, abolish any claims of infliximab inducing and maintaining disease remission in isolation. In those sufferers who do not respond to infliximab infusion, repeat administration will be of no additional benefit.¹⁴ Similar caution in prescribing should be observed in those patients who have antinuclear antibodies at baseline, as this subgroup are approximately twice as likely to develop anti-dsDNA antibodies.

Clinicians and patients have welcomed infliximab, when alternative pharmacological approaches have been exhausted. The concerns regarding the cost of prescribing may be short lived, since infliximab represents the first of a number of anti-TNF- α treatments under investigation, some of which may prove to be more economically viable options.

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