

# Infliximab: the evidence for its place in therapy in ulcerative colitis

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## Abstract

**Introduction:** Refractory ulcerative colitis has a high, unmet medical need for avoiding steroid dependency and avoiding colectomy. Controlled trials with biologic agents have recently been reported.

**Aims:** We aimed to review the current evidence supporting the use of the monoclonal antitumor necrosis factor antibody, infliximab, in active ulcerative colitis and determine its current place in therapy.

**Evidence review:** Although faced with initial conflicting data particularly in steroid-refractory patients, two large, placebo-controlled trials have shown that intravenous infliximab induces and maintains clinical improvement in a clinically significant proportion of patients when used with scheduled re-treatment. Infliximab also spares steroids and induces endoscopic remission in moderately ill patients. In fulminant colitis unresponsive to intravenous steroids, one placebo-controlled trial indicates that infliximab is able to prevent colectomy in this patient population. Evidence for cost effectiveness and avoidance of colectomy long term are still lacking.

**Place in therapy:** Infliximab 5 mg/kg induction at 0, 2, and 6 weeks, and every 8 weeks thereafter should be considered in patients with moderately to severely active ulcerative colitis failing medical therapy. Steroid-dependent and steroid-refractory patients also qualify for infliximab therapy.

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**Key words:** biologic agents, fulminant colitis, infliximab, mucosal healing, ulcerative colitis

## Core evidence place in therapy summary for infliximab in moderate to severe ulcerative colitis

Outcome measure	Evidence	Implications
<b>Patient-oriented evidence</b>		
Improvement of symptoms	Clear	Improved disease control
Maintenance of clinical response	Clear	Improved disease control long term
Sparing of steroids	Clear	Prevention of steroid-induced complications in corticoid-dependent patients
Prevention of colectomy	Moderate	Substantial evidence on short-term efficacy; long-term data awaited
Improvement in quality of life	Limited	Reduced hospitalizations
Efficacy superior to steroids	Limited	No controlled comparative trials available; uncontrolled trials suggesting equivalence
<b>Disease-oriented evidence</b>		
Endoscopic healing of mucosal lesions	Clear	Biologic endpoint reflecting reduced colonic inflammation and increased mucosal repair
Induction of T-cell apoptosis	No evidence	Apoptosis induction as a mechanism of action for biologics has not been established in ulcerative colitis
Prevention of colonic dysplasia	No evidence	Mucosal healing is associated with a decreased risk of dysplasia, but no data are available for infliximab
<b>Economic evidence</b>		
Cost effectiveness as an alternative to corticosteroid therapy	No evidence	Long-term pharmacoeconomic studies missing
Cost effectiveness as an alternative to calcineurin inhibitors or colectomy in fulminant colitis	No evidence	Long-term colectomy avoidance data missing

Scope, aims, and objectives

Despite the therapeutic efficacy of the biologic agent infliximab (Remicade®) in Crohn’s disease, the development of agents specifically interacting with an immune pathway has not led to registered novel therapeutics in ulcerative colitis (UC). Recently more biologic agents have entered development programs in this indication but contrary to the situation in Crohn’s disease, many of these programs have originally been driven by interest from investigators involved in patient care and not by the pharmaceutical industry. Several reasons may underlie this discrepancy in “market interest” between Crohn’s disease and UC. First, the immunopathogenesis of UC is ill-defined and this hinders the selection of a clear target pathway. The lack of paradigm about cytokines driving the inflammatory reaction in UC prevents extrapolation to other diseases such as rheumatoid arthritis, spondyloarthropathy, or psoriasis, as is the case for Crohn’s disease. Finally, colectomy with ileal pouch anastomosis is viewed by many as a good solution for refractory UC even with all the possible long-term inconveniences associated with this procedure.

Although the pathogenesis of UC is incompletely understood, several lines of evidence justify the development of antitumor necrosis factor (anti-TNF) agents in the medical management of UC. Until 2 years ago, most of the data had originated from uncontrolled studies, but three large, placebo-controlled trials have recently demonstrated that for moderate to severe UC and for fulminant steroid-refractory UC, the anti-TNF agent infliximab has clinical efficacy. This review will discuss the scientific rationale for using anti-TNF agents in UC and will address the current evidence supporting a role for infliximab in inducing and maintaining clinical improvement in active UC.

Methods

English language literature searches were conducted in the following databases, searching from the beginning of the database to date unless otherwise stated. The search strategy was “infliximab AND ulcerative colitis” unless otherwise stated (Table 1):

- PubMed, <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>
- Web of Science, <http://scientific.thomson.com/products/wos>
- Cochrane Database of Systematic Reviews (CDSR), <http://www.cochrane.org/index0.htm>

Disease overview

Inflammatory bowel diseases (IBD) are chronically relapsing intestinal inflammatory conditions with a typical onset in young adulthood and with an unpredictable disease course that may lead to debilitating complications. Crohn’s disease and UC are the two main phenotypes of IBD. These chronic immune-mediated disorders are characterized by abdominal symptoms

Table 1   Evidence base included in the review		
Category	Number of records	
	Full papers	Abstracts
Initial search	268	0
records excluded	243	
records included	25	
Additional studies identified	32	1
Total records included	57	1
Level 1 clinical evidence (systematic review, meta analysis)	1	0
Level 2 clinical evidence (RCT)	5	1
Level ≥3 clinical evidence	20	1
Economic evidence	0	0
For definitions of levels of evidence, see Editorial Information on inside back cover or on Core Evidence website. RCT, randomized controlled trial.		

(diarrhea, abdominal pain, rectal bleeding) and systemic manifestations (arthralgia, fatigue, dermatologic and biliary complications). The most pertinent difference between the two illnesses is the disease location. Crohn’s disease typically occurs in the terminal ileum (terminal enteritis) and right-sided colon. However, lesions can appear anywhere in the gut and the disease frequently affects different parts of the intestine with skip areas of uninvolved mucosa (regional enteritis). UC, on the other hand, most often involves the rectum and extends over a variable distance in the colon. Two-thirds of patients have only left-sided colonic disease with sparing of the right colon. Also, Crohn’s disease is a transmural disease leading to fistulas and intestinal strictures, whereas UC only affects the colonic mucosa and submucosa.

While UC can present at any age, patients are often diagnosed in young adulthood, which means that this disease is associated with a high psychologic and socioeconomic burden. The diagnosis is based on the clinical presentation, on findings at colonoscopy, and on histologic findings in mucosal biopsies. The course of UC is notably unpredictable at diagnosis. Some patients have smoldering disease with few symptoms and occasional flares, but others have signs of severe systemic inflammation and debilitating diarrhea with abdominal cramps, necessitating aggressive medical management. Fifteen to twenty percent of patients will develop fulminant colitis necessitating hospitalization and intravenous therapy during the course of their disease. Complications include toxic megacolon, profuse colonic bleeding, and colorectal cancer.

UC is relatively infrequent with an estimated incidence of five per 100 000 in the US, Canada, Australia, South Africa, and northwestern Europe. Latin and South America, southern Europe, and the rest of the world appear to have a much lower incidence. However, since UC is a lifetime illness, peak prevalences of one in 500 have been reported. At present most patients need to be treated long term (several decades).

### Role of TNF in the pathogenesis of UC

Although UC, like Crohn's disease, is a chronic inflammatory disorder of unknown origin, some elements in the cascade driving the inflammatory reaction and the tissue damage in the colonic mucosa and submucosa have been elucidated. In contrast to Crohn's disease, which is characterized by a predominant T-helper-1 cytokine profile with secretion of cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-gamma), the uncontrolled tissue damage in the mucosa and submucosa of UC patients appears to be fostered by humoral immunity with antibody-secreting plasma, T lymphocytes with a T-helper-2 cytokine profile, and neutrophils. Plasma cells isolated from the gut wall of UC patients produce copious amounts of immunoglobulin G (IgG) and complement-activating IgG1 antibodies are preferentially secreted (Halstensen et al. 1993). Also, autoantibodies directed against endogenous proteins such as tropomyosins are secreted in the serum of UC patients, corroborating the role of humoral, B-cell-mediated immunity in UC (Das et al. 1993). Despite these apparent differences in lymphocyte subtypes driving the inflammatory reaction in Crohn's disease and UC, the effector phase of the immune response in both types of IBD is characterized by the secretion of similar inflammatory cytokines such as TNF and IL-1-beta. Indeed, several lines of evidence support the development of anti-TNF agents to treat patients with active UC. In inflamed mucosa, in the serum, and in the stools of both Crohn's disease and UC patients the proinflammatory cytokines IL-1, IL-6, and TNF predominate. More specifically, TNF immunoreactive cells are increased in the lamina propria of UC and Crohn's disease patients (Murch et al. 1993). This phenomenon is found in both adults and children with IBD, although in children the TNF increase is particularly elevated in Crohn's disease (Murch et al. 1993; Breese et al. 1994). Intraluminal TNF levels obtained by colonic lavage are increased in active but not in endoscopically quiescent UC (Casellas et al. 1994). Serum TNF levels are markedly elevated in patients with UC, and patients with active disease have a 1.7-fold higher level than patients with inactive disease (Komatsu et al. 2001). Furthermore, an imbalance in the secretion of TNF and neutralizing soluble TNF receptors favoring the secretion of TNF has been observed in culture supernatants of colonic biopsies from patients with active colitis (Noguchi et al. 1998). Moreover, the TNF-alfa converting enzyme (TACE), which serves to activate and release TNF from the cell membrane, is specifically increased in colonic biopsies of UC patients as compared to biopsies from patients with Crohn's disease or healthy individuals (Brynskov et al. 2002). Indeed, in the cotton-top tamarin animal model of UC, humanized anti-TNF antibodies ameliorate the spontaneous colitis (Watkins et al. 1997).

In Crohn's disease a clear defect in apoptosis of lamina propria and circulating T cells has been reported (Ina et al. 1999); also, in UC, deficiencies in T-cell apoptosis have been observed (Boirivant et al. 1999). Anti-TNF agents may act in IBD through the induction of T-cell apoptosis or through restoration of defective apoptosis rather than through simple neutralization of soluble or membrane-bound TNF. In Crohn's disease, *ex-vivo* and recently also *in-vivo* evidence points to this hypothesis (Lügering et al.

2001; Van den Brande et al. 2003; Shen et al. 2007). In UC the relative role of apoptosis induction relative to TNF neutralization for the efficacy of anti-TNF antibodies needs further study. Antimetabolite immunosuppressives such as azathioprine and 6-mercaptopurine also may act by inducing T-cell apoptosis or by inhibiting T-cell proliferation in patients with UC.

Although the data on the role of TNF in the pathogenesis of UC have not been unequivocal, taken together they suggest that TNF contributes to the mucosal damage and chronic inflammation responsible for signs and symptoms of active UC (Table 2).

**Table 2 | Preclinical evidence supporting use of infliximab in ulcerative colitis patients**

Evidence	Reference
Increase in mucosal TNF immunoreactive cells	Murch et al. 1993
Increased TNF levels in mucosa, serum, and stools	Murch et al. 1993; Casellas et al. 1994; Komatsu et al. 2001
Stool TNF levels specifically increased in endoscopically active UC	Casellas et al. 1994
Imbalance favoring TNF over neutralizing soluble TNF receptors	Noguchi et al. 1998
Specific increase in TNF-activating enzyme	Brynskov et al. 2002
TNF, tumor necrosis factor; UC, ulcerative colitis.	

### Current therapy options

The medical management of UC should be tailored to the disease severity in every individual patient. Mild UC can usually be managed with oral 5-aminosalicylates (mesalamine or sulfasalazine). Since recent evidence suggests that 5-aminosalicylates have a dose-dependent effect in UC above a daily dose of 2 g, higher doses of these compounds are generally used because they are well tolerated. For patients with moderate disease (interfering with activities of daily life) refractory to medical therapy, oral systemic steroids (at an initial dose of 40 mg of prednisolone equivalent) have been proven to induce clinical improvement and remission. However, systemic steroids have a high burden of side effects when used long term and are only used in courses of 3 to 4 months. Steroid-dependent patients (those not being able to taper steroid therapy or needing several courses of systemic steroids within 1 year) are therefore a key target for drug development in UC. Patients who have achieved a steroid-induced remission can return to 5-aminosalicylate maintenance or start antimetabolite therapy (e.g. methotrexate). Patients who have not responded to a 2- to 4-week course of oral systemic steroids (at an initial dose of 40 mg prednisolone equivalent or higher) are usually considered to fail oral steroids (steroid-refractory) and need other treatment options.

### Rectal therapy

Rectal therapy with 5-aminosalicylates offers clinical benefit for fast relief of symptoms and increases disease remission and

endoscopic healing. Ambulatory patients with moderate disease who continue to have symptoms of left-sided disease despite an adequate course of oral mesalamine may benefit from rectal mesalamine and/or rectally administered topical steroids to alleviate their urgency and rectal blood loss. Rectal mesalamine at a once-daily dose of 1 to 4 g is superior to rectal steroids for treating distal disease and should always be considered as the first option (Marshall & Irvine 1997). Rectal mesalamine therapy also results in a more rapid and better disease control in patients with extensive disease (Marteau et al. 2005).

### Immunosuppressives

The purine analogs azathioprine and 6-mercaptopurine have a steroid-sparing effect in patients with UC responding to corticosteroids but are not a treatment option for patients failing these agents since they require 2 to 4 months of therapy at adequate doses to produce a clinical effect. The folate antagonist methotrexate has not proven to be efficacious in a randomized trial to treat patients with moderately active steroid-refractory UC. Recently, evidence from an uncontrolled open-label trial has suggested a role for oral methotrexate in the treatment of moderate UC (Cummings et al. 2005), but patients should know that a 6- to 8-week lag phase is to be expected before this treatment is efficacious.

Oral cyclosporine at a starting dose of 5 mg/kg with subsequent adjustment of trough levels to therapeutic ranges has been proposed to treat patients with refractory UC based on results in open-label studies (Actis et al. 1999; Navazo et al. 2001). The other calcineurin inhibitor used in solid organ transplantation, tacrolimus, given at an initial dose of 0.1 mg/kg has also been reported in open-label trials to be efficacious in this setting (Fellermann et al. 2002; Baumgart et al. 2006), given for a median of 2 years in one of the patient cohorts (Baumgart et al. 2006). Recently, a placebo-controlled Japanese study confirmed the efficacy of high-dose tacrolimus in active colitis, with controlled dosing to give a trough level of 10–15 ng/mL (Ogata et al. 2006). However, both cyclosporine and tacrolimus are considered nephrotoxic when used long term at these dose levels and attempts to interrupt treatment after a period of 3 months is usually made. Given the current evidence and the lack of long-term safety data, oral tacrolimus and cyclosporine should be regarded as “bridge” therapy, since azathioprine typically has a delayed onset of action and an induction agent is needed to cover the first 3 to 6 months.

### Fulminant colitis

Only 15–20% of patients with UC will ever experience an attack of fulminant colitis requiring in-hospital management (Edwards & Truelove 1963). Patients with pancolitis appear to be predisposed to severe flares. Fulminant UC is a serious, potentially life-threatening condition and hospitalization should be considered in all patients with severe attacks. Even if patients have been treated with oral corticosteroids for the ongoing flare, intravenous corticosteroids at a dose equivalent to prednisolone 60 mg should be considered. Pioneering studies by Truelove et al. have shown

that by applying this strategy, 64% of patients will enter clinical remission and only 23% require total proctocolectomy (Truelove et al. 1978). Regardless of the treatment strategy these patients require intensive attention by a surgical-medical team experienced in dealing with severe colitis.

When patients fail 3 to 5 days of intravenous corticosteroids at adequate doses, and continue to report frequent bloody diarrhea with fever or high C-reactive protein levels, they should be considered for total proctocolectomy or rescue medical treatment (Travis et al. 1996). Complications such as toxic megacolon or uncontrolled bleeding should favor surgical intervention.

Intravenous cyclosporine has been shown to be an effective rescue therapy for severe UC attacks in three controlled trials (Lichtiger et al. 1994; D’Haens et al. 2001; Van Assche et al. 2003). In the trial by Lichtiger et al., nine out of 11 patients treated with intravenous cyclosporine 4 mg/kg avoided colectomy, versus none of the nine placebo-treated patients. Data from one single-center controlled trial in 73 patients indicate that intravenous cyclosporine 2 mg/kg per day as initial treatment may prove effective for severe attacks of UC, although not all of these patients were failing intravenous corticosteroids. When results from controlled and uncontrolled trials are pooled, 76–85% of patients will respond to intravenous cyclosporine and avoid colectomy in the short term, with a median time to response of 4 to 5 days (Van Assche et al. 2003). In responding patients, initiation of oral cyclosporine therapy at 5–8 mg/kg divided into two daily doses should be considered along with gradual steroid tapering and initiation of azathioprine or 6-mercaptopurine. However cyclosporine use in UC has been associated with mortality, mostly as a result of opportunistic infections (Arts et al. 2004). Following initial response to cyclosporine for fulminant UC, about 50% of patients avoid colectomy at 3 years (Cohen et al. 1999; Arts et al. 2004; Campbell et al. 2005; Moskovitz et al. 2006). Lower colectomy-free rates have been recently reported with follow-up extending to 7 years (Moskovitz et al. 2006). The patient population already failing adequate courses of azathioprine or 6-mercaptopurine is most prone to colectomy following initial response to cyclosporine (Moskovitz et al. 2006). However, cyclosporine is only administered in 3-month courses to patients with IBD. This probably explains why patients failing azathioprine are more prone to early colectomy after initial response to cyclosporine since no adequate exit strategy can be provided. Oral cyclosporine and tacrolimus can be considered to treat severe attacks of UC, but only retrospective uncontrolled data are available for UC and the one controlled trial with oral tacrolimus included ambulatory, less severe patients (Baumgart et al. 2006; Ogata et al. 2006). Surgical proctocolectomy with ileo-anal pouch anastomosis is a valid option for patients with moderate to severe UC failing medical therapy. Patients should be counseled about the option of surgery, and the short-term complications and long-term outcomes of pouch surgery early in the course of a severe flare of UC. The important need for colectomy (at least 50% after 5 to 7 years) despite initial successful medical management and the considerable toxicity of cyclosporine therapy, emphasizes the active and early role of the surgical team in the management of patients with UC. Early

decision-making and timely colectomy can prevent surgical complications and save patient lives, and should always be considered.

### Unmet needs

The main unmet medical needs in UC are in patients with moderate to severe disease failing 5-aminosalicylates and more importantly corticosteroids, and also patients with corticosteroid-dependent disease, who are at high risk of major side effects from steroid therapy. In fulminant colitis, colectomy can be prevented in the short term by intravenous corticosteroids, and by cyclosporine in steroid-refractory patients, but long-term disease control and salvage from colectomy is substantially reduced despite the association of antimetabolite therapy. More specifically, in patients failing adequate therapy with azathioprine or 6-mercaptopurine, steroids and cyclosporine are of limited value since they offer no long-term perspective. Also surgical proctocolectomy, although a good solution for patients with intractable disease or neoplasia, has several limitations including pouchitis, postoperative obstruction, frequent stools, and reduced female fecundity. Complications occur only in a small proportion of patients, but cannot be predicted prior to the procedure.

Therapeutic potential can therefore be expected from therapies that meet all or most of the following aims:

- Induction and maintenance of symptomatic remission in a high proportion of patients
- Sparing of corticosteroids
- Induction of endoscopic mucosal healing
- Prevention of surgery and avoidance of surgical complications if colectomy is needed
- Long-term, highly beneficial benefit-to-risk ratio, including the risk of colonic dysplasia.

In an attempt to address these needs and utilize the role of TNF in UC pathogenesis, a number of anti-TNF agents have been investigated.

CDP-571 is a humanized, anti-TNF, IgG4 antibody that has been evaluated in an open-label trial, and shows some improvement in clinical scores although the effect was short-lived (Evans et al. 1997). A total of 15 patients with mild to moderate, mostly left-sided disease were included. In these patients a significant reduction in the mean Powell-Tuck scores was observed as soon as 1 week after infusion of CDP-571 at 5 mg/kg, although the endoscopic scores did not improve. The development of CDP-571 has been halted.

RDP58 has been rationally designed to block the translation of several cytokines such as TNF, IL-2, and IL-12. It is an interesting small molecule that inhibits the production of several cytokines

including TNF at a posttranscriptional level and has been studied in patients with moderately active UC. In a randomized trial patients received placebo, or RDP58 100, 200, or 300 mg daily for 4 weeks (Travis et al. 2003). Both higher doses resulted in high clinical remission rates (72% and 70% vs 40% in placebo-treated patients). Also, histologic scores decreased more in RDP58-treated patients. In this trial the placebo remission rate of 40% was exceptionally high. Nevertheless, the drug appeared to be safe and is appealing due to its oral route of administration and its very low absorption. This low systemic bioavailability could have favorable implications for the side effect profile.

Infliximab has been investigated in patients with UC, and forms the focus of this review.

## Clinical evidence for the use of infliximab in UC

### Infliximab in adult UC

#### Open-label studies

The first reports on the use of the chimeric, humanized, anti-TNF, IgG1 antibody infliximab in Crohn's disease date back to 1995 and the compound has changed the treatment paradigm for this illness. In UC, infliximab has been evaluated initially in several open-label trials for refractory, moderate to severe disease. The open-label trial experience with infliximab treatment for moderately to severely active UC has generated conflicting results to say the least (Table 3). Differences in patient populations and the lack of strict diagnostic criteria at baseline only partially account for this discrepancy. Differences in clinical scores used to evaluate disease and in study endpoints (response vs remission) are also only part of the explanation. As suggested in several editorials, a strong placebo response for patients receiving an intravenous treatment with proven high efficacy in Crohn's disease may have influenced the judgment of both patients and investigators (Rutgeerts 2002; Cohen 2003).

A US, multicenter, open-label trial involving 27 patients (mostly outpatients despite 89% having severe disease) investigated one to three infusions of infliximab 5 mg/kg (Chey et al. 2001). Remission was observed in 44% of patients and another six patients (22%) had a partial response. The median time to response was 4 days and the median response duration 8 weeks. Most nonresponding patients underwent colectomy. Interestingly, steroid-refractory patients were less likely to respond than those responding but relapsing during steroid tapering (33% vs 83%).

Subsequently, several papers describing open-label trial experience with infliximab were published. These trials have generated opposing data on putative efficacy but no important safety concerns have arisen. Bermejo et al. (2004) reported on the use of infliximab in seven patients with disease refractory to standard treatment. Of the six patients with steroid-dependent disease, five (83%) responded both clinically and endoscopically. Similarly, Kohn et al. (2002) reported on the success of infliximab treatment in 13 patients admitted to a Turin academic hospital. The retrospective analysis showed that clinical response was obtained in 77% of infliximab-treated patients. A similar high



**Table 3 |** Summary of outcomes with infliximab in adult ulcerative colitis patients

Design	No. of patients	Baseline steroid use	Key outcomes	Reference
Placebo controlled	43	All patients steroid refractory	Infliximab not superior to placebo	Probert et al. 2003
Placebo controlled	45	All patients i.v. steroid refractory	Infliximab superior to placebo	Järnerot et al. 2005
Placebo controlled	728	30% steroid refractory	Infliximab (5 and 10 mg/kg) superior to placebo	Rutgeerts et al. 2005
Active comparator, open label	20	Steroid-refractory patients excluded	Efficacy comparable to oral steroids	Armuzzi et al. 2004
Active comparator, open label	13	Steroid-refractory patients excluded	Efficacy comparable to oral steroids	Ochsenkühn et al. 2003
Placebo controlled, early termination	11	All patients i.v. steroid refractory	50% infliximab response, 0% placebo response	Sands et al. 2001
Open label, retrospective	16	All patients steroid refractory	88% response	Chey et al. 2001
Open label	27	Improved response rates in steroid-responsive disease	66% response, 44% remission	Su et al. 2002
Open label, retrospective	7	6/7 steroid responsive	5/6 response (all steroid responsive)	Bermejo et al. 2004
Open label, retrospective	13	All patients i.v. steroid refractory	77% response rate	Kohn et al. 2002
Open label, retrospective	8	All patients steroid refractory	50% immediate colectomy, 4/6 response	Actis et al. 2002
Open label, retrospective	6	All patients steroid refractory	6/6 improvement, 4/6 remission	Kaser et al. 2001

i.v., intravenous.

clinical response rate in all six steroid-refractory patients treated with intravenous infliximab has also been observed (Kaser et al. 2001). In contrast, Actis et al. (2002) showed a short-term colectomy rate of 50% and a sustained response rate of only 25% in eight steroid-refractory patients treated with infliximab in an open-label study.

*Level 2 evidence*

These conflicting results achieved in open-label studies needed to be challenged or confirmed in controlled studies. In 2003 the results of a European, double-blind, randomized, controlled trial with infliximab in steroid-resistant UC were published. This trial enrolled 43 patients with active UC colitis resistant to oral glucocorticosteroids (prednisolone  $\geq 30$  mg) (Probert et al. 2003). Endoscopically active disease was present in all subjects at inclusion. The Barron endoscopic score was used in this trial which includes roughly the same criteria as more recently developed scores (e.g. Mayo score, mentioned below). Mucosal friability, erosions and ulcers, and fading of the vascular pattern constitute the key criteria of most of these endoscopic scores.

Patients were treated at weeks 0 and 2 with intravenous infliximab 5 mg/kg or placebo. At 6 weeks no difference in clinical remission was observed between infliximab- and placebo-treated patients (39% vs 30%). Also, the median improvement in the Barron endoscopic activity score or the proportion of patients achieving a score of 0 (endoscopic remission) was not different between both groups (endoscopic remission 26% with infliximab vs 30% with placebo). Patients were offered open-label intravenous infliximab 10 mg/kg once and every 8 weeks thereafter if they did not respond after 6 weeks, but the investigators were not unblinded at this time point. Of the patients treated in this open-label phase with infliximab, remission was achieved in 27% (3/11) and 11% (1/9) of the original infliximab and the placebo groups,

respectively. No differences in the occurrence of serious adverse events were noted and one patient in the placebo group had a colectomy during the intervention period.

Two large multicenter trials sufficiently powered to assess the true therapeutic potential of infliximab in active, moderate to severe UC have now been published (Rutgeerts et al. 2005). The Active Colitis Trials, ACT-1 and ACT-2, enrolled 728 patients in 171 centers worldwide. Each of the trials recruited patients with clinically and endoscopically active disease. Patients were randomized to receive infliximab 5 mg/kg, infliximab 10 mg/kg, or placebo at week 0, 2, and 6 and then every 8 weeks thereafter for 22 weeks (ACT-1) or 46 weeks (ACT-2) in total. Apart from the duration of treatment, the main difference between the two trials was the fact that patients in ACT-2 were allowed to fail only mesalamine whereas in ACT-1 only patients failing steroids and/or purine analogs were eligible. All these drugs were continued for the entire treatment phase of the two trials, except for steroids, which were tapered from week 8. Efficacy assessment was based on an intention-to-treat analysis and the primary endpoint was clinical response at week 8 based on the Mayo disease activity score (Schroeder et al. 1987). This score has been developed to assess the efficacy of mesalamine and encompasses criteria of stool frequency, rectal bleeding, findings at endoscopy, and physician's global assessment (Table 4). Again, the clinical criteria used in the Mayo score are based on the clinical activity index developed earlier and used in other trials with infliximab in UC. The score can vary between 0 and 12, and patients with scores of 6 to 10 inclusive were eligible. Endoscopic activity of at least 2 (loss of vascular pattern and at least mucosal erosions) on the Mayo scale was also a necessary inclusion criterion. The primary endpoint of clinical response was defined as a decrease of at least 3 points and at least 30% in the total Mayo score. Secondary endpoints were clinical remission (total Mayo score of 2 points or lower with a maximum of 1 in any of the subscores)

and endoscopic healing (endoscopic score of 0 or 1). Baseline characteristics of the patients in both ACT-1 and ACT-2 were very similar in both trials. More than half of patients (56%) entered the trials on steroid therapy (60% on prednisolone <20 mg) and less than half were on immunosuppressives (46%). Early discontinuation, mostly due to aggravation of colitis, occurred twice as frequently in placebo-treated patients.

**Table 4 | Mayo scoring system for active ulcerative colitis** (reproduced with permission from Schroeder et al. *N Engl J Med.* 1987;317:1625–1629. Copyright © 1987 Massachusetts Medical Society. All rights reserved.)

Score	Description
<b>Stool frequency</b>	
0	Normal number of stools for this patient
1	1–2 stools more than normal
2	3–4 stools more than normal
3	5 or more stools than normal
<b>Rectal bleeding<sup>a</sup></b>	
0	No blood seen
1	Streaks of blood with stool less than half of the time
2	Obvious blood with stool most of the time
3	Blood alone passed
<b>Mucosal appearance</b>	
0	Normal or inactive disease
1	Mild disease (erythema, decreased vascular pattern, mild friability)
2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulceration)
<b>Physician's global assessment</b>	
0	Normal
1	Mild disease
2	Moderate disease
3	Severe disease

<sup>a</sup>Most severe bleeding of the day determines the score.

In ACT-1, the clinical response at week 8 (following a three-dose induction with infliximab) was 69% and 62% for patients receiving infliximab 5 and 10 mg/kg, respectively, compared with 37% of those receiving placebo ( $P<0.005$  for both comparisons). In ACT-2, very similar results were obtained, with 65% and 69% of patients receiving infliximab 5 and 10 mg/kg, respectively, achieving a clinical response at week 8, compared with 26% in the placebo group ( $P<0.001$  for both comparisons). In both studies, the proportion of patients who achieved clinical response at weeks 8, 30, or 54 (ACT-1) or clinical remission at weeks 30 or 54 (ACT-1) was several-fold higher among infliximab-treated patients than placebo-treated patients. At week 54, 16% of patients on placebo, 35% on infliximab 5 mg/kg, and 34% on 10 mg/kg were in remission ( $P=0.001$  for both comparisons). Sustained remission at week 8, 30, and 54 was observed in fewer patients, but again significant differences were observed between

the placebo- (7%) and infliximab-treated groups (20%) in ACT-1. Endoscopic mucosal healing was also significantly more frequent in infliximab recipients. At week 8, approximately 30% of placebo-treated compared with 60% of infliximab-treated patients had complete mucosal healing or only mild lesions, and this difference remained significant at week 30 in both ACT-1 and ACT-2, and at 54 weeks in ACT-1.

A recent Cochrane analysis concluded that there is level 1 evidence to support the efficacy of infliximab in UC based mainly on the ACT-1 and ACT-2 trial results (Lawson et al. 2006). The relative risk versus placebo to be in clinical remission with intravenous infliximab 5 mg/kg at weeks 0, 2, and 6 was 3.2 [95% confidence interval (CI) 2.18, 4.76].

Furthermore, infliximab produced clear steroid-sparing effects. In ACT-1, the median prednisolone dose decreased from 20 mg at baseline to 8.5 mg at week 54. Despite the steroid-sparing potential, however, only 21% of patients were in clinical remission and off steroids at 1 year. This indicates that one in three patients in remission still had some degree of steroid therapy, but the figures compare well with data observed in Crohn's disease maintenance trials with anti-TNF agents (Hanauer et al. 2002). As in Crohn's disease, the 10 mg/kg dose appeared to offer no additional clinical benefit over the 5 mg/kg dose of infliximab.

#### Evidence from active comparator trials

Recently, two small, open-label, randomized trials were initiated to explore the efficacy of infliximab compared with oral corticosteroids in patients with active disease not failing steroids. A first study enrolled 20 patients with moderate to severe (Mayo score  $\geq 6$ ) disease to receive infliximab 5 mg/kg intravenously at 0, 2, and 6 weeks and every 8 weeks thereafter, or corticosteroids 0.7–1 mg/kg for 1 week followed by gradual tapering (Armuzzi et al. 2004). Preliminary results showed that all patients (10/10) in both groups achieved clinical remission. After a median of 10 months' follow-up, 9/10 of the infliximab group and 8/10 of those on corticosteroids were still in clinical remission. Patients who relapsed were successfully treated either with infliximab at shorter intervals of 6 to 4 weeks (initial infliximab group) or with infliximab at 0, 2, and 6 weeks (steroid group).

Ochsenkühn et al. (2003) also reported preliminary data from an open-label, randomized trial comparing intravenous infliximab 5 mg/kg given at week 0, 2, and 6 ( $n=6$ ) with high-dose prednisolone 1.5 mg/kg ( $n=7$ ) for inducing remission in active UC not failing steroids. Clinical response was achieved in 5/6 of the infliximab- and in 6/7 steroid-treated patients.

#### Infliximab in fulminant colitis

An initial report by Chey et al. (2001) showed an extremely high efficacy in 16 patients with severe disease. In seven of these patients infliximab was used as a rescue therapy to avoid colectomy. After a single infliximab 5 mg/kg infusion, 88% of patients responded with a marked clinical and endoscopic improvement. Successful steroid tapering was possible in most

patients and sustained clinical improvement was observed for at least 4 months.

Consecutively, a placebo-controlled, multicenter trial was terminated prematurely due to slow patient enrollment. The study was scheduled to enroll 60 patients in severe, active, steroid-refractory UC, but eventually enrolled just 11 patients; eight in the infliximab group (5, 10, or 20 mg/kg for one infusion) and three in the placebo group (Sands et al. 2001). Four patients treated with infliximab improved after 2 weeks versus none receiving placebo. The precise implication of these data is hard to define due to the limited size of the patient population.

More recently the results of a Scandinavian placebo-controlled trial confirmed the initial findings. In this trial, patients with moderate to severe UC failing to respond to hospital treatment with intravenous steroids (betamethasone 4 mg/day) were randomized to receive infliximab 5 mg/kg in one infusion or placebo (Järnerot et al. 2005). Patients were eligible either because of fulminant colitis [assessed with the Sweden index (Seo et al. 2002)] at day 4 after starting intravenous steroids, or because they had more moderate disease activity but failed to improve from day 4 until day 8. Mesalamine therapy was started or continued in all patients and azathioprine was initiated at the discretion of the investigator. In total 45 patients were included, of whom 24 received infliximab, over a period of 3.5 years. Sixty-two percent of patients in both groups were included on the basis of the fulminant colitis index in both groups. Of note, more patients in the placebo group were experiencing their first attack of UC (43% vs 12% in the infliximab group).

The primary endpoint of the trial was defined as colectomy or death within 90 days from baseline. Significantly more patients in the placebo group met this endpoint (67% vs 29%,  $P < 0.02$ ; odds ratio 4.9; 95% CI 1.4, 17). The cumulative proportion of patients not needing colectomy after 90 days was 71% in the infliximab group versus 33% in the placebo group ( $P < 0.05$ ). Interestingly, the difference in colectomy rates between the two groups was not significant for the patient groups recruited on the basis of fulminant disease activity at day 4, but only for those with more moderate disease at that time point. Severe endoscopic lesions at baseline, however, were not associated with poor prognosis.

In summary, this trial provides evidence of the potential of infliximab to prevent colectomy in hospitalized patients with steroid-refractory UC, but long-term outcome data on the patient population included in this trial are needed to define the precise role of infliximab in the setting of fulminant colitis.

### Safety of long-term infliximab therapy

Biologic agents are selective and powerful therapies for patients with IBD. Although the experience with infliximab has shown a beneficial benefit-to-risk ratio, some specific complications need to be addressed (Table 5).

The chimeric nature of the monoclonal antibody infliximab gives rise to antibodies to infliximab (ATIs) in humans. ATIs are

associated with acute infusion reactions and loss of response, and with delayed hypersensitivity reactions and secondary loss of response. Acute infusion reactions are manifested by shortness of breath, chest pain, palpitations, flushing, headache, and sometimes urticaria and hypotension. They are in most cases easily managed with slowing of the infusion and administration of antihistamines and/or hydrocortisone. Patients who have experienced acute infusion reactions should receive prophylactic hydrocortisone before subsequent infusions. The delayed infusion reactions or serum sickness-like reactions occur typically 4–9 days after an infusion and are characterized by arthralgias (which may include unusual locations such as the jaw), back pain, myalgias, fever, skin rash, and leukocytosis. These delayed reactions need management with high doses of steroids for 4–7 days.

The risk of serious infections, particularly with intracellular pathogens such as *Mycobacterium tuberculosis* is increased in infliximab-treated patients and has been related to mortality. In patients with Crohn's disease and rheumatoid arthritis, no clear increase in lymphoma incidence has been found in controlled clinical trials. A recent meta analysis of clinical trials with infliximab and adalimumab for rheumatoid arthritis suggested an increased risk of malignancy in patients receiving higher ( $\geq 6$  mg/kg) doses of infliximab (odds ratio 4.3; 95% CI 1.6, 11.8) (Bongartz et al. 2005). For patients treated with infliximab in rheumatoid arthritis, the number needed to harm was 59 for serious infections, and 154 for malignancy. From clinical trials and from postmarketing surveillance, no increased risk of malignancy has become apparent with the use of infliximab (Biancone et al. 2006; Lichtenstein et al. 2006). Nevertheless, infliximab in combination with azathioprine has been associated with rare cases of gamma/delta T-cell hepatosplenic lymphoma in 10 young patients, nine of whom had Crohn's disease, and one with unclassified colitis (Anon. 2007). Although it is impossible to define the relative role of both drugs in these lymphoma cases, they illustrate the need for postmarketing safety surveillance. In this respect, the North American TREAT registry has not revealed an increased risk for malignancies related to the use of infliximab in patients with Crohn's disease thus far (Lichtenstein et al. 2006). An *in-silico* model of the benefit-to-risk ratio with the use of infliximab based on experience in clinical trials and in large patient cohorts came up with a beneficial effect of an infliximab-based strategy over non-infliximab-based management. More specifically, surgery-free remission was clearly increased in the putative infliximab-treated patient group. However, this came with the price of an increased mortality and lymphoma risk (Siegel et al. 2006).

In the ACT-1 and ACT-2 trials the total number of adverse events and the proportion of patients with adverse events was similar in placebo- and infliximab-treated patients (Rutgeerts et al. 2005). The proportion of patients with a serious adverse event or with an infectious event was also similar in the three groups, but in ACT-1 significantly more patients in the combined infliximab group had an infectious event necessitating antibiotic treatment. In both studies combined, four neoplasias were found in the infliximab-treated patients versus one in the placebo



**Table 5 | Complications associated with the use of biologic agents in inflammatory bowel diseases<sup>a</sup>**

Disease mechanism	Clinical equivalent	Drugs observed with	Preventive strategies
Immunosuppression	Infections, malignancy	Infliximab Adalimumab, certolizumab-pegol Natalizumab	Screening for latent infections Physicians' awareness
Immunogenicity	Loss of response Infusion reactions	Infliximab MLN-02 Natalizumab	Humanization of therapeutic Ab Systematic maintenance treatment Concomitant immunomodulators/steroids
Induction of autoantibodies	Drug-induced lupus arthralgias	Infliximab	Screening past history Physicians' awareness
Demyelination neurotoxicity	Central/peripheral neuropathy Optic neuritis	Infliximab	Screening past history Physicians' awareness
Toxicity in diseased cardiac muscle	Progressive cardiac failure	Infliximab	Contraindicated in NYHA grade III–IV cardiac failure

<sup>a</sup>Only infliximab has been approved by the Food and Drug Administration and European Medicines Agency for use in ulcerative colitis. Data for this agent are deducted from clinical trial and postmarketing experience. The risk of malignancy in patients treated with biologic agents is still debated and so far no increase over the incidence in the general population has been formally documented.  
NYHA, New York Heart Association.

group. Neurologic events occurred in three infliximab recipients and one patient exposed to infliximab developed drug-induced lupus.

Patients with UC resistant to intravenous steroids enrolled in the Scandinavian controlled trial had no specific safety issues when exposed to infliximab (Järnerot et al. 2005). Of note, two patients in the placebo group had a septic complication after colectomy, which confirms the association of postoperative complications with high-dose steroids rather than with infliximab or purine analogs.

UC carries a limited but intrinsic risk of colorectal cancer, which is thought to develop from dysplasia originating in chronically inflamed mucosa. Since one of the aims of medical therapies such as anti-TNF agents is to prevent colectomy, particularly in patients with fulminant disease, saving the colon may expose patients to a higher dysplasia risk in the long term. On the other hand, mucosal healing and regression of inflammation, as has been shown with anti-TNF therapy, should counterbalance this increased risk of neoplasia (Rutter et al. 2004, 2006). Also, the risk of colorectal cancer in patients with longstanding UC reported in recent patient cohorts is considerably lower than what has been reported before (Jess et al. 2006). This observation cannot be explained by increased colectomy rates, but the exact role of improved disease control with medical therapy in the apparent decrease of the cancer risk is also not clear. The dysplasia and rectal cancer cases in the ACT trials both occurred in infliximab-treated patients, but the trials were not powered to study the influence of infliximab on rare events such as dysplasia. In patients with fulminant colitis, particularly those with pancolitis, the risk of developing cancer when the colon is saved and preserved long term, has not been specifically studied and cannot be weighed against surgical morbidity with colectomy. As long as this question remains unresolved, it appears prudent to apply surveillance programs to patients with longstanding UC controlled with any form of medical therapy, including anti-TNF antibodies.

## Resource utilization

No published data on direct assessments of resource utilization with the use of infliximab in UC are known to the authors. However, the ACT-1 and ACT-2 trials show that scheduled maintenance therapy with infliximab for 1 year reduces the need for hospitalization (Rutgeerts et al. 2005). Hospitalization and surgery contribute heavily to the cost of treatment in these patients. There appear to be no long-term data on colectomy rates in patients successfully treated with infliximab. Total colectomy abolishes the need for further treatment in UC patients and most patients have a good quality of life after colectomy. Since biologic agents such as infliximab weigh significantly on the direct drug cost to induce remission in UC patients, further studies exploring prevention of hospitalization and colectomy, of the ability to work, and of added quality-adjusted life-years are crucial. These outcomes have been achieved with infliximab in Crohn's disease, but specific data are needed in patients with UC.

## Dosage, administration, and fomulations

The label for infliximab for use in patients with moderate to severe UC granted by both the European Medicines Agency and the Food and Drug Administration allows both induction and maintenance therapy in patients with treatment-refractory active colitis. Induction therapy consists of intravenous infliximab 5 mg/kg at week 0, 2, and 6. In scheduled maintenance therapy, infliximab is administered intravenously at a dose of 5 mg/kg every 8 weeks. Studies in Crohn's disease have shown that scheduled maintenance is superior to periodic therapy during disease flare in the prevention of immunogenicity to the chimeric antibody, and is considered the optimal strategy (Hanauer et al. 2002; Rutgeerts et al. 2004; Sands et al. 2004). However, no direct comparison between the two modalities of treating patients long term has been performed in UC.

## Place in therapy

Although the clinical development of anti-TNF agents in Crohn's disease has clearly outpaced the progress in UC, a lot of progress has been achieved in recent years. The role of anti-TNF in the effector phase of the inflammatory reaction in both UC and Crohn's disease provides a scientific rationale to investigate the therapeutic potential of anti-TNF agents in UC. However, the initial data obtained in retrospective and prospective open-label trials yielded conflicting results. More recently, data from two large, controlled trials with infliximab in patients with moderate to severe UC has clearly shown clinical efficacy of the antibody to induce clinical response and remission short term and long term, to induce and maintain mucosal healing, and to spare steroids. Moreover, the first fully conducted, randomized controlled trial in patients with fulminant steroid-refractory UC has demonstrated that infliximab is efficacious at inducing clinical improvement and at preventing colectomy. Outstanding issues in patients with fulminant colitis are associated with the relative role of infliximab and cyclosporine in medical management. In general, it appears that the same rules for timing of infliximab and cyclosporine therapy should be followed (initiation after 3–5 days of unsuccessful intravenous steroid therapy). No trials comparing the relative efficacy of both drugs are available at present. Also, data on the use of infliximab in patients failing cyclosporine or vice versa are extremely scant. Theoretical concerns have arisen about the long half-life of a monoclonal antibody in patients considered for additional immunosuppressive therapy, but prospective safety data are lacking.

Since the patient population included in the large ACT-1 and ACT-2 trial was quite heterogeneous, a more broad population may be eligible for treatment. It is clear that 5-aminosalicylates will remain first-line therapy for mild to moderate UC. Patients with moderate disease failing oral corticosteroids, who are dependent on corticosteroids, or who are considered for their second course of steroids within 6 months after failing the previous course should be considered for infliximab therapy. Previous antimetabolite therapy should not prevent infliximab therapy since in ACT-1 and ACT-2 such patients were clearly responding. Although not all patients achieve clinical remission with infliximab, it should influence clinical practice particularly in patients with refractory disease. No new safety issues specific for UC patients have arisen from the combined experience reported in the literature, but the side effect profile of anti-TNF agents should be known to every clinician using this potent therapy.

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