

# Is there any place for the chimeric antibody against tumor necrosis factor (infliximab) in the treatment of patients with active ulcerative colitis?

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## SUMMARY

We attempt to summarize the current aspects concerning the role of the chimeric antibody against tumor necrosis factor-alpha (Infliximab – Remicade) in patients with active ulcerative colitis. Experimental and clinical data suggest that, apart from Crohn's disease, tumor necrosis factor also plays quite an important role in the pathogenesis of ulcerative colitis as well. So far, there are limited data on the use of infliximab in animal models of ulcerative colitis and in patients with ulcerative and indeterminate colitis and pouchitis. Although the existing clinical, endoscopic and laboratory evidence for the efficacy of infliximab in the treatment of ulcerative colitis are controversial, we can support the assumption that a proportion of patients may benefit from this treatment. In addition, treatment with infliximab appeared to be well-tolerated at the doses studied. Further, ongoing, controlled studies are investigating the potential efficacy and safety of infliximab in patients with active ulcerative colitis.

**Key words:** Infliximab, Remicade, Ulcerative colitis, Inflammatory bowel disease

## 1. INTRODUCTION

Ulcerative colitis is a chronic relapsing inflammatory condition involving the large bowel, of unknown etiology. Clinical manifestations are considered to be the result of an imbalance between proinflammatory and inflammatory cytokines, resulting in inflammation and clinical symptoms. Activated T-lymphocytes release cytokines, thereby recruiting a large number of inflammatory cells in the mucosa. Activation of these cells causes further production of cytokines, cell recruitment, and inflammation. In addition to cytokines, leukotrienes, thromboxane and reactive oxygen species are released from activated mucosal cells<sup>1</sup>. This uncontrolled immune system activation results in the sustained overproduction of reactive metabolites of oxygen and nitrogen<sup>2</sup>. It has been suggested that self-sustaining cycles of oxidant formation may amplify flare-ups of inflammation and mucosal injury in ulcerative colitis<sup>3</sup>.

Tumor necrosis factor-alpha (TNF- $\alpha$ ) plays quite an important role in a number of inflammatory disorders including Crohn's disease and ulcerative colitis<sup>4</sup>. It has been shown that administration of the chimeric anti-TNF- $\alpha$  antibody in patients with active Crohn's disease, results in a dramatic improvement of many clinical, endoscopic and laboratory parameters<sup>5,6</sup>.

Recently, there has been active debate, concerning the role of this antibody in the treatment of patients with ulcerative colitis. However, the exact role of this antibody in ulcerative colitis patients has not yet been elucidated, despite the fact that relevant reports have appeared in the international literature.

In this review, the current discussion concerning the possible role of infliximab in active ulcerative colitis is

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critically analyzed and reviewed.

## 2. ROLE OF TNF- $\alpha$ IN THE PATHOGENESIS OF ULCERATIVE COLITIS

TNF- $\alpha$  is a 17-kD proinflammatory cytokine produced by monocytes, macrophages and T-cells. The biological actions of this important cytokine include induction of acute-phase response, cachexia, and potentially lethal shock<sup>7</sup>. Furthermore, TNF- $\alpha$  stimulates the secretion of interleukins such as IL-1 and IL-6, chemokines such as IL-8 and MCP-1, upregulates the expression of adhesive molecules and has been identified as a major metalloproteinases (MMPs) inducing cytokine<sup>8</sup>.

It has also been shown that TNF- $\alpha$  is a cofactor in stimulating the production of the inflammatory cytokines gamma-Interferon and IL-2 by T-cells<sup>9,10</sup>.

Release of TNF- $\alpha$  is mediated by a specific metalloproteinase (TNF- $\alpha$  convertase). After secretion, TNF- $\alpha$  binds - as a soluble ligand - to two cell-bound transmembrane TNF receptors, namely TNFR1 and TNFR2. Soluble TNF neutralizes TNF activity, acting as a natural TNF inhibitor. Cell death, altered target gene transcription and cytokine production is mediated by TNFR1. TNFR2 promotes cell proliferation and cell survival by antiapoptotic effect, acting through a nuclear factor kappa B pathway<sup>11</sup>.

Chronic inflammation in Crohn's disease can be attributed mainly to the production of proinflammatory cytokines, especially TNF- $\alpha$ , which is considerably increased in the histologically normal as well as inflamed large bowel mucosa of Crohn's disease patients<sup>12</sup>.

In UC, it has been felt that the cell-mediated inflammatory process is not as significant a player in the local mucosal inflammation, and that the Th-2 helper T cell dysregulation somehow allows for the production of humoral (antibody) factors that cause inflammation, produces cell necrosis and the mucosal damage noted in ulcerative colitis<sup>8</sup>.

However, preclinical and clinical data suggest an important role for TNF- $\alpha$  in the pathogenesis of ulcerative colitis (UC). Serum TNF- $\alpha$  concentration and colonic TNF- $\alpha$  mRNA expression level are increased significantly in UC rats and this increase has been shown to correlate with the severity of disease<sup>13</sup>. Both CD4+ and CD8+ lymphocytes participate in the development of experimental TNBS-induced colitis and both Th1 and Th2 cells are involved<sup>14</sup>.

Patients with UC have demonstrated increased concentrations of serum TNF- $\alpha$  and Interleukin-6 (IL-6) which decreased with remission of the disease<sup>15-17</sup>. Studies of colon biopsy specimens from patients with active UC have demonstrated increased concentrations of TNF- $\alpha$  in the lamina propria and enhanced secretion of TNF- $\alpha$  by lamina propria mononuclear cells, with the extent of secretion closely correlated with the intensity and severity of local mucosal inflammation<sup>18,19</sup>.

It has recently been reported that thalidomide, a drug with well-known anti-TNF- $\alpha$  action, significantly reduces the colonic inflammation induced by iodoacetamide, probably via inhibition of TNF- $\alpha$ <sup>20</sup>.

Rodent models of chronic colitis have shown that compounds such as anti-TNF- $\alpha$  antibodies, which down-regulate the production or activity of these inflammatory cytokines, are able to reduce the severity of intestinal inflammation<sup>21,22</sup>.

In the cotton-top tamarin (*Saguinus oedipus*), a spontaneous illness closely resembling human ulcerative colitis frequently develops in captivity. Animals treated with CDP571, an antibody to TNF- $\alpha$  gained weight, showed a reduction in disease activity and had reproducible improvements in histology scoring<sup>23</sup>.

In the first report of anti-TNF antibody in the treatment of ulcerative colitis, 15 patients received open label treatment with CDP571. A significant reduction in the clinical activity of the disease was noted one week after infusion<sup>24</sup>.

Consequently, from the existing data we can assume that TNF- $\alpha$  probably plays an important role both in experimental and human ulcerative colitis.

Infliximab (Remicade) is the first example of a biological response modifier used in the treatment of inflammatory bowel disease it is a chimeric (75% human, 25% murine) IgG1 monoclonal antibody directed against TNF. Proposed mechanisms of action for infliximab include neutralization of both soluble and transmembrane TNF, as well as lysis of TNF producing cells via complement fixation, antibody dependent cytotoxicity and apoptosis of T lymphocytes caused by the IgG1 Fc portion of the antibody<sup>25</sup>.

## 3. USE OF INFLIXIMAB IN EXPERIMENTAL COLITIS

There are limited data on the use of Infliximab in experimental colitis in rats<sup>26,27</sup>. Triantafillidis et al (paper

submitted 2004)<sup>26</sup> found that the subcutaneous administration of Infliximab reduces the inflammatory activity, as well as tissue TNF- $\alpha$  and manolaldehyde levels in an experimental model of chemical colitis in rats. It was found that Infliximab in a dose of 5 mg/kg achieves better histological results and produces higher reduction of the levels of TNF- $\alpha$  compared to Infliximab of 10 mg/Kg. Furthermore, Infliximab 5 mg/Kg produces higher reduction of tissue manolaldehyde levels to compared Infliximab 15 mg/Kg. The above mentioned results are in accordance with the clinical results obtained on patients with severe active or fistulazing Crohn's disease.

Woodruff et al<sup>27</sup> also found significant improvement in the parameters measured on a rat model of inflammatory bowel disease after a single dose pretreatment with infliximab.

#### 4. EFFICACY OF INFLIXIMAB IN ULCERATIVE COLITIS PATIENTS

##### 4.1 Clinical trials

The first clinical indication of the potential role of infliximab in UC was observed in two steroid-resistant UC patients who were treated with Remicade and experienced a rapid clinical response, with healing of lesions noted in one of the patients<sup>28</sup>.

Based upon these results a randomized, placebo-controlled, double-blind Phase II trial was conducted to evaluate the efficacy, safety, and tolerability of infliximab at a dose of 5, 10, or 20 mg/Kg, or placebo, in patients with severe UC, refractory to IV corticosteroid therapy<sup>29</sup>. Only 11 patients (of 60 planned) were enrolled in this study and the study was terminated prematurely due to poor recruitment. The primary end-point was treatment failure at the week-2 evaluation and the study period was 12 weeks.

At week 2, none (0%) of the 3 placebo-treated patients and 4 of the eight (50%) infliximab-treated patients were considered treatment responders. All the placebo-treated patients underwent colectomy by the week-2 evaluation. During the follow-up period, two patients who received 5 mg/Kg and 10 mg/Kg of infliximab and were classified as treatment failure underwent colectomies. Another patient who received 5mg/kg infliximab and was classified as a treatment responder at week-2 evaluation underwent colectomy between weeks 2 and 3 after the infusion.

Treatment with infliximab was well tolerated. However, all 11 patients in this trial experienced at least

one adverse event most of which were mild or moderate in intensity. The most frequently reported adverse events were pruritus, headache, and urinary tract infection. In this study the remission rate was not reported and no statistical analysis was offered by the authors because of the small number of patients.

In another study, Chey et al presented the initial results of 8 patients treated with a single infusion of 5mg/kg of infliximab<sup>30</sup>. The patients had active ulcerative colitis refractory to usual combination medical therapy and many of these patients were scheduled for surgical colectomy because of their active disease. During the course of treatment all patients had tried 5-amino-salicylates, in doses of up to 4 g per day, parenteral steroids, but had not responded satisfactorily. Additionally, 6 of 8 were on 6-mercaptopurine.

All eight patients had resolution or significant improvement of most of their clinical symptoms by 1 week after the infusion of Infliximab. A significant histological improvement in colonic biopsies taken before and after treatment was also reported.

The same authors, in an extension of the previous study, presented the results of sixteen patients with severely active, treatment-refractory UC<sup>31</sup>. Seven of these 16 patients (44%) were scheduled to undergo colectomy. Patients received at least one 5 mg/Kg dose of Infliximab, with a second infusion being administered as needed. Six of the 16 patients (38%) received a second infusion approximately 5 months after the first.

Clinical response was achieved in 88% of patients after infusion of the first dose (5mg/kg) of infliximab and was maintained in 14/16 (88%) for more than 4 months and in 4/16 (25%) for 7 to 10 months. Six out of seven patients who were potential surgical candidates were able to avoid colectomy. Nine of the 16 patients were successfully treated with infliximab in an outpatient treatment unit and avoided hospitalization. Ten out of 13 patients were successfully withdrawn from steroids, demonstrating a steroid-sparing effect.

In an open-label pilot study, Kaser et al<sup>32</sup> described the treatment of 6 patients with severe, steroid-refractory UC with a single infusion of infliximab 5 mg/Kg in an open label pilot study. All patients experienced dramatic improvement by day 7 following infliximab treatment. Clinical activity scores according to Lichtiger scale decreased from 16.3 to 4.8 at day seven ( $P < 0.0001$ ). Colonoscopy confirmed significant healing of endoscopic lesions. Two patients had relapsed by week 4 however 4 patients had long-term remission with a median follow-

up of 5.5 months.

Fleisher et al<sup>33</sup> evaluated the use of infliximab 5 mg/Kg at 0, 2, and 6 weeks in 17 steroid-naive moderate to severe UC patients. Patients were refractory to mesalamine. For those in remission, infliximab re-treatment was administered every 2 months. The remission rates induced by infliximab ranged from 80% to 100% at 4 weeks, and 80% to 86% at 8 and 12 weeks.

Actis et al examined the efficacy of infliximab in 8 patients with severe steroid-refractory ulcerative colitis<sup>34</sup>. The patients received an intravenous dose of infliximab 5mg/kg. Clinical response was observed in 4 patients (50%). The other 4 patients underwent an urgent colectomy.

Two of the responders have maintained clinical remission for 7 months, without the need for steroids; both were on azathioprine and one received two further infliximab infusions. Of the other two, one received a second infusion at week 5, but relapsed and underwent elective colectomy at that time and the other relapsed at 6 months and showed a partial response to a repeat infliximab infusion. Thus the rate of sustained response is 2/8 (25%) in this study.

Kohn et al evaluated the efficacy of infliximab in the treatment of severe ulcerative colitis refractory to conventional therapy in an open label study<sup>35</sup>. Thirteen patients with severe ulcerative colitis refractory to therapy with methyl-prednisolone 60mg daily for more than 7 days were treated with a single infusion of infliximab 5 mg/kg.

Of these 13 patients, 10 (77%) had a clinical response, 2 (15%) had a colectomy whilst 1 patient refused surgery and was lost to follow-up. All patients who responded showed a very rapid clinical improvement within 2 to 3 days of infusion. The mean time of follow-up was 10.1 months (range 5-12). During this time 9 out of 10 patients (90%) maintained clinical remission and were able to discontinue corticosteroid therapy.

More recently Su et al<sup>36</sup> described the use of Infliximab in UC patients from four different IBD centres. Twenty-seven patients were included in this study of which 24 (89%), 2 (7%) and 1 (4%) had severe, moderate and mild disease respectively. All patients had previously been treated with steroids. Yet, 10 (37%) remained steroid dependent and 9 (33%) were steroid refractory. In addition, 9 patients (33%) were receiving at least one immunomodulator (i.e. mercaptopurin, azathioprine, methotrexate, cyclosporine) at the time of infliximab therapy. 52% and 48% of patients received a single or

multiple infusions (range 2 to 15), respectively. The most common interval between infliximab infusions was 6-8 weeks.

Twelve patients (44%) achieved remission after treatment with infliximab. Six (22%) and 9 patients (33%) had a partial or no response to infliximab therapy. The median time interval from the infliximab therapy to clinical response and remission was 4 days (range 1 to 21 days).

All but three patients (n = 24) were followed up to at least 1 month after infliximab therapy. The median duration of follow-up was 4 months (range, 4 days to 16 months). Six months after the initial infusion, 50% of patients were in remission and 10% experienced clinical response. The median duration of response to single infliximab infusion was 8 weeks and remained constant with subsequent infusions. Nine of the 18 patients who responded experienced 19 relapses, 95% of which were successfully treated with repeat infusions. Five of the non-responders underwent total proctocolectomy 6 to 40 days after the last Infliximab infusion.

It is of interest that concurrent use of corticosteroids or immunomodulators was not associated with a higher degree of clinical response. Another interesting observation was that steroid refractory patients were less likely to respond to infliximab therapy than were steroid-responsive patients (33% vs 83%, p=0.026). Of the 10 steroid-dependent patients, steroid withdrawal or reduction in dose was achieved in 90%.

Serious adverse events were reported in two patients. One patient died one day after undergoing a total proctocolectomy (10 days after receiving a second dose of Infliximab). His death was attributed to central venous line sepsis and subacute bacterial endocarditis. Another patient developed candidemia 4 days after undergoing total proctocolectomy and ileostomy for severe refractory UC. Two infusions of Infliximab had been administered 7 and 14 days prior to colectomy. The fever resolved after administration of antibiotics and removal of the central line.

However, quite to the contrary, the randomized, double-blind, placebo controlled study of Probert et al<sup>37</sup> does not support the use of Infliximab in the treatment of moderately severe steroid-resistant UC. In this study, 43 steroid resistant patients, on 30 mg prednisolone (or equivalent) for at least one week, were randomized (20:23) to receive a blinded infusion of Infliximab 5 mg/Kg (n=23) or placebo (n=20) at weeks 0 and 2. At screening, an ulcerative colitis symptom score of 6 or

more, and a sigmoidoscopy score of at least 2 on Baron's scale was required. Disease activity, quality of life, CRP levels, change in daily glucocorticosteroid dose and safety were assessed over 8 weeks of follow-up.

After 6 weeks, remission was observed in 39% of the infliximab-treated group compared to 30% in the placebo group ( $P=NS$ ). No statistical difference was found between groups in quality of life, sigmoidoscopic assessment of disease activity and CRP levels. The mean reduction in daily dose of steroids in the infliximab group was 19 mg compared to 14 mg in the placebo group ( $P=0.037$ ).

The authors concluded that their data does not support the use of infliximab in the management of unselected steroid-resistant patients with ulcerative colitis. The small advantage of infliximab in glucocorticoid sparing deserves further exploration in controlled trials.

#### 4.2 Case reports

Several case reports<sup>38-41</sup> also described the use of Infliximab in the treatment of UC, the results of which are shown in table 1. Although the number of cases described so far is limited, it could be argued that some degree of benefit could be expected from the administration of infliximab.

### 5. EFFICACY OF INFLIXIMAB IN INDETERMINATE COLITIS

So far in the literature only two studies deal with the efficacy of infliximab in medically refractory indeterminate colitis.

Papadakis et al<sup>42</sup> have recently described the results of infliximab administration (5 mg/Kg) in 20 patients with medically refractory indeterminate colitis. The number of infusions ranged from one to 16 per patient. Clinical remission was defined as complete, partial or non-

response. Fourteen out of 20 patients (70%) showed a complete response to infliximab treatment, two showed a partial response and 4 showed no response. The four non-responders underwent colectomy with ileal pouch-anal anastomosis.

It is of interest that two out of four resected large bowels showed a histological picture compatible with Crohn's disease. Eight additional patients were subsequently reclassified as having Crohn's disease in longer follow-up evaluation, whilst eight continued to have features of indeterminate colitis. The response rate to Infliximab treatment was similar in both groups. The authors concluded that infliximab is effective in almost  $\frac{2}{3}$  of patients with indeterminate colitis and thus is indicated in these patients prior to decision of colectomy.

Gornet et al<sup>43</sup> retrospectively evaluated 30 patients treated with infliximab 5 mg/Kg for UC ( $n=19$ ) or indeterminate colitis (11 patients). Infliximab was initiated because patients experienced steroid resistance ( $n=18$ ), dependence ( $n=5$ ) or intolerance ( $n=7$ ). Patients received either a single ( $n=17$ ) or up to 3 infusions ( $n=13$ ). Response and remission rates were assessed at day 7 and 1 month following first infliximab infusion.

At day 7, 21 out of 28 patients (75%) experienced a response, with 43% having complete remission. At month 1, 14 out of 28 (50%) had a response and 32% experienced complete remission. Among the responders, the probability of relapse was 73% at month 6. The probability of complete remission without steroids, taking into account the retreatment for relapse ( $n=11$ ), was 38% at month 3 and 57% at month 6. The probability of colectomy was 33% at month 12. In indeterminate colitis, the response rate was only 50% at day 7 and 30% at month 1. Nine patients experienced adverse events. Four patients experienced an infection, which resolved in all cases.

The authors concluded that infliximab was able to induce a rapid response in some patients with ulcerative colitis or indeterminate colitis refractory to conventional treatment. Long term results were less favorable, with frequent relapses and about one-third of the patients required a colectomy.

### 6. EFFICACY OF INFLIXIMAB IN POUCHITIS

Viscido et al<sup>44</sup> studied 7 patients with refractory pouchitis complicated by fistulae (pouch-bladder, vaginal, perianal, and vaginal-perianal) erythema nodosum was present in 4 patients. The possibility of Crohn's disease

**Table 1.** Results of Infliximab administration on patients with severe active UC (Case- reports)

Author	Year	Single infusion	Multiple infusions	Outcome	Duration of follow-up
Bagnato	2002	Yes	remission	8 wks remission	No
Mahmoud	2002	Yes	remission	1 year remission	NM
Unzueta	2002	Yes	no improvement	colectomy	
Lam	2003	Yes	improvement	colectomy	NM

NM= Not mentioned

was excluded after careful reexamination of all clinical and histological parameters. Patients received infliximab at 0, 2 and 6 weeks. Azathioprine (2.5 mg/Kg) was started for all patients. Clinical response was classified as complete, partial or no response.

Clinically, all patients improved. Six out of 7 patients showed complete response at the 10 week follow-up. The fistula was closed in 5 cases. A significant improvement of pouchitis activity index was noticed. Erythema nodosum disappeared after the first infusion of Infliximab. It seems that Infliximab could be of benefit in patients with refractory pouchitis complicated by fistulae following ileal pouch-anal anastomosis for ulcerative colitis.

Colombel et al<sup>45</sup> studied 26 patients with ileal pouch-anal anastomosis who were found to have Crohn's disease in the follow-up period. Patients received one to three infusions of infliximab over 8 week as induction therapy. Subsequently they received a variable number of maintenance infusions. The authors concluded that infliximab may be of benefit in both short and long-term treatment of patients with an ileal pouch-anal anastomosis performed for a presumed diagnosis of ulcerative colitis, who subsequently develop Crohn's disease-related complications.

## 7. DISCUSSION - CONCLUSION

Severe UC is potentially life threatening, even though in recent years have intensive medical treatment and early colectomy reduced mortality to almost zero. Intravenous steroids are still the mainstay of medical treatment although the maximal duration of administration, before stating that such a treatment has failed has not been clearly defined<sup>46</sup>.

Steroid resistance represents a major clinical problem in the treatment of inflammatory bowel disease and affects up to 30% of patients with severe ulcerative colitis. Given the established efficacy of infliximab in Crohn's disease, it was inevitable that the efficacy of infliximab in ulcerative colitis would be tested.

Most of the existing data on the efficacy of infliximab in ulcerative colitis arise from open label, uncontrolled studies that are open to bias. In addition, the use of clinical response instead of remission as an end point in many of these studies is another problem. However the reasonable expectation for any new treatment should be to induce remission of the disease and to make a difference in the long-term follow up of the patients. The

clinical, endoscopic, and laboratory evidence of a reduction in disease activity that has been observed in a proportion of patients treated with infliximab cannot be ignored.

In a recent randomized, double blind, placebo-controlled trial, treatment with infliximab showed no significant difference in remission rates compared to placebo, although there was a small advantage of infliximab in glucocorticoid sparing. The authors commented that the study may have been inadequately powered to be sure that there is no clinically relevant benefit from infliximab.

Inferentially, from the available clinical studies we can't define the role of infliximab in the therapy of ulcerative colitis. Further controlled studies are ongoing to investigate the potential efficacy and safety of infliximab treatment in ulcerative colitis.

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