CLINICAL–ALIMENTARY TRACT

Infliximab as Rescue Therapy in Severe to Moderately Severe Ulcerative Colitis: A Randomized, Placebo-Controlled Study

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Background & Aims: **Despite treatment with corticosteroids, severe to moderately severe attacks of ulcerative colitis have a high colectomy rate. We intended to find a rescue therapy other than cyclosporin A, which imposes a high risk of side effects and cyclosporine-related mortality.** ***Methods:*** **This was a randomized double-blind trial of infliximab or placebo in severe to moderately severe ulcerative colitis not responding to conventional treatment. Patients were randomized to infliximab/placebo either on day 4 after the initiation of corticosteroid treatment if they fulfilled the index criteria for fulminant ulcerative colitis on day 3 or on day 6–8 if they fulfilled index criteria on day 5–7 for a severe or moderately severe acute attack of ulcerative colitis. Results were analyzed according to the intention-to-treat principle. The primary end point was colectomy or death 3 months after randomization. Secondary end points were clinical and endoscopic remission at that time in patients who did not undergo operation.** ***Results:*** **Forty-five patients were included (24 infliximab and 21 placebo). No patient died. Seven patients in the infliximab group and 14 in the placebo group had a colectomy (P = .017; odds ratio, 4.9; 95% confidence interval, 1.4–17) within 3 months after randomization. No serious side effects occurred. Three patients in the placebo group required operation for septic complications.** ***Conclusions:*** **Infliximab 4–5 mg/kg is an effective and safe rescue therapy in patients experiencing an acute severe or moderately severe attack of ulcerative colitis not responding to conventional treatment.**

Traditionally, acute attacks of ulcerative colitis (UC) have been treated intensively with high doses of corticosteroids intravenously (IIVT). Despite IIVT, severe attacks had a high colectomy rate varying from 38% to 47% in 2 frequently quoted series.[1,2] Of patients with UC affecting the entire colon, 60% had surgery within 3 months.[2] Also, a moderately severe attack was associated with a risk for operation in approximately 20% of the patients.[2]

Cyclosporin A (CyA) was shown to be an effective rescue therapy in acute attacks of UC not responding to steroids.[3] However, this increases the risk of side effects[4] and of CyA-related mortality.[5,6] For this reason, CyA has not been adopted as rescue therapy for patients with failed steroid treatment in Sweden and most Danish centers, because the risks were considered greater than those for surgical therapy.

Infliximab (Remicade; Centocor Inc, Malvern, PA) has become an established treatment in Crohn's disease (CD). It is a chimeric monoclonal antibody to human tumor necrosis factor (TNF)-α that is constructed by linking the variable regions of a mouse antihuman TNF mono-

Abbreviations used in this paper: CI, confidence interval; CRP, C-reactive protein; CyA, cyclosporin A; OR, odds ratio; TNF, tumor necrosis factor.

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clonal antibody to human immunoglobulin G1 with light κ chains.[7] TNF-α has also been shown to play an important role in the inflammatory process in UC. Increased levels of TNF-α have been found in feces from patients with active UC.[8,9] The TNF-α reactivity in UC was most pronounced subepithelially, whereas in CD expression it has also been found deeper in the mucosa or submucosa.[10] The correlation between TNF-α expression and the histological findings was good but was less so with the endoscopic appearance.[11] Normally the inflammatory response to an increased TNF-α production is counteracted by inhibitors. One study strongly indicated that in inflammatory bowel disease, the production of TNF-α inhibitors is down-regulated.[12]

Thus, there is good theoretical evidence to test infliximab also in acute attacks of UC. Only 1 small placebo-controlled study has been published, and it was stopped because of slow enrollment.[13] Three uncontrolled studies support the effect of infliximab in acute attacks of UC.[14–16] In a prospective uncontrolled study, 8 of 11 (73%) patients with severe UC similar to those included in the present placebo-controlled study escaped immediate colectomy.[16]

Methods

Study Design

This study engaged patients with an acute severe or moderately severe attack of UC that did not respond quickly to IIVT. The study had a parallel design so that half of the patients were randomized to additional treatment with infliximab to the ongoing corticosteroid therapy, and the other half were randomized to additional placebo.

Clinical Indices

The Seo index[17] for the preceding day was calculated from the following formula

$$60 \times \text{blood in feces} + 13 \times \text{bowel movements/day} + 0.5 \times \text{ESR} - 0.4 \times \text{Hb(g/l)} - 1.5 \times \text{albumin(g/l)} + 200,$$

where ESR indicates erythrocyte sedimentation rate and Hb indicates hemoglobin. Constants were as follows: for blood in feces, 0 indicated none and 1 indicated present; for bowel movements, 0 indicated 0–3; 1 indicated 4; 2 indicated 5–7; and 3 indicated ≥8. A value <150 corresponds to remission or mild UC, 150–220 corresponds to moderately severe UC, and >220 corresponds to severe UC.

The fulminant colitis index[18] was calculated on day 3 after the institution of IIVT according to the following formula:

$$\text{number of bowel movements/day} + (0.14 \times \text{CRP} > 8\text{mg/L}),$$

where CRP indicates C-reactive protein. Seventy-two percent of patients with a value ≥8.0 had a colectomy.

Patients

Only patients with a definite or strong suspicion of UC were screened. Inclusion criteria were age 18–75 years, a diagnosis of certain or probable UC verified by a typical clinical history, appearance on endoscopy, and exclusion of an infectious cause. At hospitalization, patients had a severe or moderately severe attack of UC according to the Seo index.[17] For treatment with infliximab/placebo, the patients had to have a fulminant colitis index[18] ≥8.0 on day 3 after institution of IIVT or a Seo index on day 5, 6, or 7 that was compatible with a severe or moderately severe attack of UC that was not responding to corticosteroid treatment.

Exclusion criteria were age <18 or >75 years, pregnancy or planned pregnancy in the next 12 months, breast-feeding unless it was stopped, known or probable Crohn's colitis, infectious colitis, ongoing infection such as an abscess, central line infection, febrile urinary tract infection, active tuberculosis, or exposure to tuberculosis. A pulmonary radiograph was to precede infliximab/placebo. If there were signs of past tuberculosis or a primary complex, prophylactic treatment against tuberculosis was to be given. PPD tests were not performed. Furthermore, multiple sclerosis, malignancy, heart failure or treated heart failure, earlier treatment with infliximab or another antibody, another disease according to the investigator's judgment, psychiatric disease, alcoholism, or anything else whereby the patient was judged incapable of completing the trial resulted in exclusion.

Recruitment and Randomization

Approximately 40 Swedish and Danish centers located within 8 hospital regions expressed an interest in participation. Finally, 9 Swedish centers and 1 Danish center, covering 7 hospital regions, recruited patients. In each of the regions, a local randomization list was placed in 1 pharmacy. Randomization, which was performed in blocks of 4, was known only by the statistician.

Patients to be treated were reported to the pharmacy with their birth number, name, and weight for correct dosing. Preparation of the solution for infusion was performed in the pharmacy and delivered to the ward to blind the investigator.

The day of hospitalization was denoted as day 0. Bowel movements and fecal blood were registered daily, and body temperature and heart rate were recorded twice daily. Blood samples were drawn for hematology, liver function tests, albumin, CRP, and erythrocyte sedimentation rate. Fecal samples were sent for analyses of possible pathogens and *Clostridium difficile* toxin, which gave the laboratory 3–4 days to finish the analysis. No sample was positive after that time. Analysis for parasites was performed when clinically indicated. Biopsies were not performed to exclude cytomegalovirus infection. A plain abdominal and lung radiograph was taken. A severity index using the criteria of Seo et al[17] was calculated on day 0. Patients with an index of >150, corresponding to severe to