

RESEARCH LETTER

Infliximab With Low-Dose Methotrexate for Prevention of Postsurgical Recurrence of Ileocolonic Crohn Disease

Postsurgical recurrence of Crohn disease is a very frequent event, and none of the drugs used for the purpose has really shown a clear-cut efficacy.¹ Infliximab, a monoclonal antibody anti-tumor necrosis factor α (anti-TNF- α), is very effective in the treatment of active Crohn disease, but its benefit in preventing postoperative recurrence is still unknown. Yet, its impact, both medical and economic, could be major.² Local injection of infliximab for early mucosal postoperative recurrence of Crohn disease seems feasible and safe; however, preliminary results have been disappointing.³ By contrast, a patient treated with intravenous infliximab immediately after surgery to prevent the recurrence of colonic Crohn disease has been disease free for 48 months after surgery.⁴

Methods. In the present prospective pilot study, infliximab was administered 2 weeks after surgery, along with low-dose methotrexate, whereas controls were treated with mesalamine alone. There is no evidence for a role of methotrexate in preventing recurrence⁵; however, we elected to use this drug because it is known to reduce long-term immunogenicity of infliximab.⁶ This is not a randomized study: the decision to include a patient in one group or the other, given the experimental nature of the infliximab-based preventive strategy, was solely based on the full understanding and approval (with written informed consent) of each patient. Before surgery, patients to be treated with infliximab were screened (purified protein derivative skin test, chest radiography, and careful history taking) and were found negative for latent tuberculosis. They were also evaluated (and found negative) for past and present cardiac, neurologic, lymphoproliferative, and other neoplastic diseases. After surgery, patients were subjected to endoscopy at 12 and 24 months; small-bowel enteroclysis or magnetic resonance imaging at 12 and 24 months; and physical examination with interviews, together with an extensive battery of blood tests (complete blood cell count; erythrocyte sedimentation rate; C-reactive protein, albumin, electrolyte, autoantibody, and thyroid hormone levels; and liver and renal function tests) every 3 months. Infliximab was given as a slow intravenous infusion at the dosage of 5 mg/1 kg of body weight, with an intravenous 100-mg bolus hydrocortisone starting from 2 weeks after surgery,

followed by standard maintenance treatment (2, 6, and then every 8 weeks) and therapy with low-dose methotrexate (10 mg/wk by mouth).

Patients in the control group were also subjected to endoscopy and small-bowel enteroclysis or magnetic resonance imaging once a year and physical examinations with interviews and blood tests every 3 months. Controls were given mesalamine-coated tablets, 800 mg 3 times daily, starting from 2 weeks after surgery.

In both groups, the use of all medications was discontinued at least a month before surgery. No other medications were allowed except for occasional tablets of paracetamol or nonsteroidal anti-inflammatory drugs. Recurrence was defined as any evidence of disease at 2 years according to simplified endoscopic or clinical criteria. In particular, clinical relapse was defined as a score of 2 or greater on the clinical recurrence grading scale (where 1 indicates absent; 2, mild; 3, moderate; and 4, severe symptoms) recently proposed by Hanauer et al,⁷ while endoscopic relapse was defined as a score of 2 or greater on the scale of Rutgeerts et al.⁸ The study protocol was approved by the institution ethics committee.

The **Table** illustrates the patients included in the study and their clinical features. Seven patients in total (3 women and 4 men) were treated postoperatively with infliximab and low-dose methotrexate. Ages ranged from 23 to 64 years (median, 36 years). Of these patients, 4 had an ileocecal resection, 1 a segmental ileal resection (he had been previously subjected to ileocecal resection), and 2 a segmental sigmoid resection (1 of these patients previously underwent ileocecal resection). Indications for resection included disease activity (2 patients) and stricture (5 patients). The disease had been present for a minimum of 3 to a maximum of 14 years (median, 7 years). Two patients currently smoke, while 1 is taking oral contraceptives.

The clinical features of the control group are also illustrated in the Table. Sixteen patients (5 women and 11 men) in total were operated on and treated postoperatively with mesalamine. Ages ranged from 23 to 70 years (median, 40.5 years). Nine patients underwent ileocecal resection (1 of whom had previously undergone segmental sigmoid resection); 1, proctocolectomy; 2, right hemicolectomy plus ileal resection; 1, left hemicolectomy; 1, cecal resection; 1, ileal resection; and 1, segmental sigmoid resection. The reason for surgery was a stricture in 8 patients, disease activity in 7, and combined stricture and disease activity in 1. The disease had been present for a minimum of 1 to a maximum of 23 years (median, 5.5 years). Four patients currently smoke, while none was taking oral contraceptives.

In all cases, surgery was considered radical (ie, it completely removed the involved intestine). Preoperative assessment (endoscopy and radiology) had excluded dis-

Table. Clinical Features of Patients With Crohn Disease and Treatment Results

Patient No./ Sex/Age, y	Disease Duration, y	Involved Intestine	Type of Surgery	Reason for Surgery	Previous Surgery	Current Smoking Status	Oral Contraceptives After Surgery	Medication Before Surgery ^a	Recurrence After Surgery at 2 y (Type of Recurrence)
Infliximab + methotrexate group ^b									
1/M/64	7	Ileocecal	Ileocecal resection	Stricture	No	No	NA	Mesalamine, prednisone cycles	No
2/M/36	3	Ileocecal	Ileocecal resection	Stricture	No	No	NA	Mesalamine, prednisone cycles	No
3/F/24	3	Sigmoid colon	Segmental sigmoid resection	Disease activity	No	No	Never	Mesalamine, prednisone cycles	No
4/F/23	9	Sigmoid colon	Segmental sigmoid resection	Disease activity	Yes	Yes, 5-6/d	No (only in the past)	Mesalamine, prednisone cycles, azathioprine	No
5/M/61	8	Ileum	Ileal resection	Stricture	Yes	Yes, 20/d	NA	Mesalamine	No
6/F/40	14	Ileocecal	Ileocecal resection	Stricture	No	No	Yes	Mesalamine, prednisone cycles	No
7/M/32	4	Ileocecal	Ileocecal resection	Stricture	No	No	NA	Mesalamine	No
Mesalamine group ^c									
1/M/47	2	Ileocecal	Ileocecal resection	Stricture	No	No	NA	Mesalamine, prednisone cycles	Yes (endoscopic and clinical)
2/F/29	1	Ileocecal	Ileocecal resection	Disease activity	No	No	No (only in the past)	Mesalamine, prednisone cycles	Yes (endoscopic)
3/F/42	19	Pancolitis	Proctocolectomy	Disease activity	No	In the past	No (only in the past)	Mesalamine, prednisone cycles, tacrolimus	Yes (endoscopic plus fistula)
4/M/49	23	Ileocecal	Ileocecal resection	Stricture	Yes	No	NA	Mesalamine, prednisone cycles	Yes (endoscopic)
5/M/41	6	Ileocecal	Ileocecal resection	Stricture	No	No	NA	Mesalamine, prednisone cycles, cyclosporin IV	Yes (endoscopic)
6/F/23	8	Ileocecal	Ileocecal resection	Stricture	No	Yes, 5-6/d	No (only in the past)	Mesalamine, prednisone cycles	Yes (endoscopic)
7/F/42	5	Ileum and right colon	Right hemicolectomy and ileal resection	Disease activity	No	Yes, 20/d	No (only in the past)	Mesalamine, prednisone cycles	Yes (endoscopic and clinical)
8/M/47	3	Cecum	Cecal resection	Stricture	No	No	NA	Mesalamine, prednisone cycles	No
9/M/34	1	Ileum	Ileal resection	Disease activity	No	No	NA	Mesalamine, prednisone cycles	No
10/F/38	7	Left colon	Left hemicolectomy	Disease activity	No	In the past	No (only in the past)	Mesalamine	No
11/M/40	1	Ileocecal	Ileocecal resection	Disease activity	No	In the past	NA	No medication	No
12/M/39	10	Ileocecal	Ileocecal resection	Stricture	No	No	NA	Mesalamine, prednisone cycles	Yes (endoscopic)
13/M/61	15	Ileocecal	Ileocecal resection	Stricture	No	Yes, 20/d	NA	Mesalamine	Yes (endoscopic)
14/M/33	1	Ileocecal	Ileocecal resection	Stricture	No	In the past	NA	Mesalamine	Yes (endoscopic)
15/M/70	6	Sigmoid colon	Segmental sigmoid resection	Disease activity	No	Yes, 5-6/d	NA	Mesalamine, prednisone cycles	Yes (endoscopic and clinical)
16/M39	1	Ileum and right colon	Right hemicolectomy and ileal resection	Disease activity and stricture	No	No	NA	Mesalamine, prednisone cycles	Yes (endoscopic and clinical)

Abbreviation: NA, not applicable.

^aThe use of every medication was stopped at least 4 weeks before surgery.

^bInfliximab, 5 mg/1 kg of body weight, was given with methotrexate, 10 mg/wk by mouth.

^cThe mesalamine dosage was 2.4 g/d.

ease outside the operated location. Of the 23 patients, none had operative or postoperative complications and none was lost to follow-up.

Results. The results, summarized in the last column of the Table, show that in the group treated postoperatively with

infliximab and low-dose methotrexate, none has had, after 2 years, endoscopic or clinical recurrence as defined in the "Methods" section. No abnormalities were detected in blood test results during the study period and at the 2-year follow-up examination. We did not record any potential adverse effect that could be attributed to these medica-

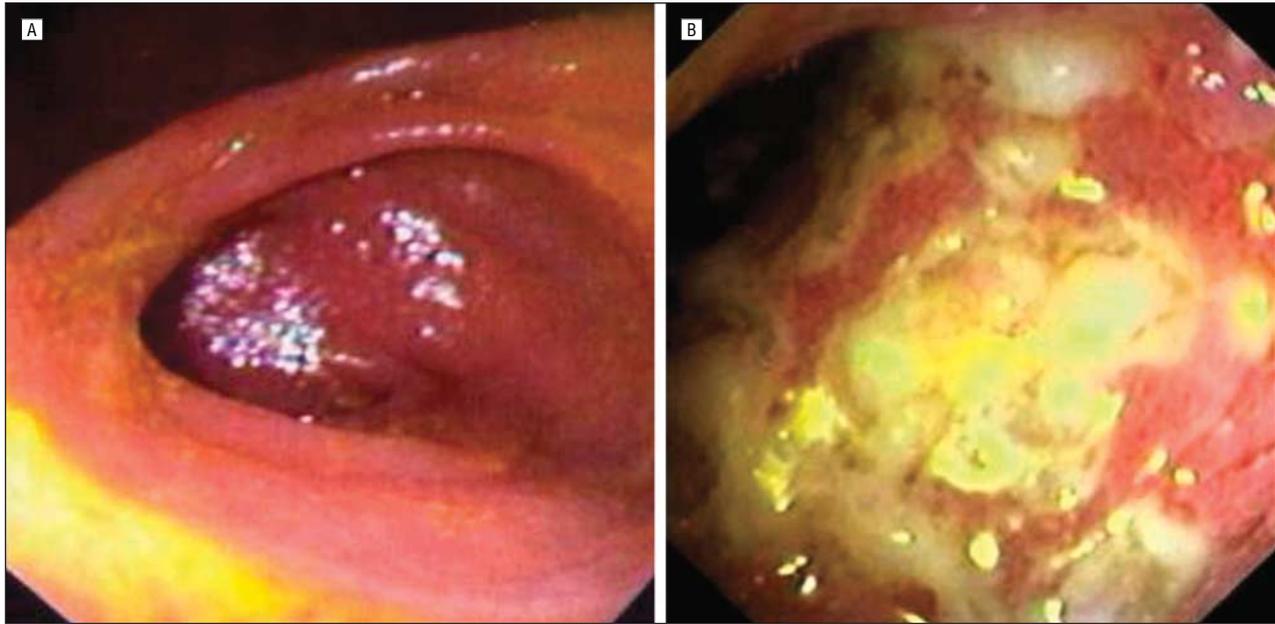


Figure. Endoscopic appearance of the mucosal anastomosis of 2 patients with Crohn disease 2 years after ileocecal resection and maintenance treatment with infliximab and low-dose methotrexate (A) or mesalamine (B). Note the complete absence of macroscopic signs of inflammation in the patient treated with infliximab and methotrexate as opposed to the extensive and large ulcerations—in a clear setting of postsurgical recurrence of Crohn disease—in the mesalamine-treated patient. The latter patient also had moderate clinical symptoms (score of 3 on the clinical recurrence grading scale [see the “Methods” section]).

tions. However, 2 patients showed transient and borderline positivity for lupus anticoagulant but none of the typical features of frank systemic lupus erythematosus, a very rare complication of infliximab treatment.⁹ All the patients in this group reported an excellent quality of life and still receive maintenance treatment.

The group treated with mesalamine also tolerated the drug well, and no adverse effects were recorded during the study period. However, in contrast to the group treated with infliximab and low-dose methotrexate, only 4 of the 16 patients (25%) were disease free 2 years after surgery. In particular, of the 12 patients with recurrent disease, 7 had endoscopic relapse, while 5 fulfilled both the endoscopic and the clinical criteria of recurrence. Of the latter patients, 1 developed a perianal fistula. Of the 12 patients with endoscopic recurrence, 9 had a score of 3 or greater on the clinical recurrence grading scale. Of the 5 patients with a clinical (as well as endoscopic) recurrence, 4 had a score of 3 or greater. Most patients with any type of recurrence had elevation of the inflammatory indexes and/or a modest to moderate decrease in hemoglobin level. These data are consistent with well-known recurrence rates recently published in the literature^{7,10} and further indicate that mesalamine is not an effective therapy to prevent recurrence.¹¹

The **Figure** shows the endoscopic appearance of the mucosal anastomosis in 2 patients 2 years after ileocecal resection and maintenance treatment with intravenous infliximab with low-dose methotrexate (A) or mesalamine (B).

Comment. Although we are well aware of the many limitations of our study (eg, lack of randomization, small sample size, and single-center experience), in our series of patients, infliximab with low-dose methotrexate was

extremely effective in preventing postsurgical recurrence of Crohn disease. Although we cannot exclude a priori an effect of methotrexate in preventing recurrence, the lack of previous evidence⁵ and the very small dose used in this study argue against it.

The results of this study reinforce the hypothesis that infliximab may actually be capable, if given early, to change the natural history of Crohn disease. We believe that a multicenter, randomized, controlled study to firmly establish the impact of this medication on the inevitability of disease recurrence¹² is warranted.

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COMMENTS AND OPINIONS

Chronic Venous Disease and Injection Drug Use

We commend Armstrong¹ for documenting the increasing age of injection drug users and relating this to the epidemiology of blood-borne pathogens. We wish to highlight other chronic complications occurring in injection drug users that have been infrequently reported. We have studied one of these conditions, chronic venous disease (CVD), extensively. Chronic venous disease causes lower extremity edema, aching discomfort, skin changes, and refractory and recurrent leg ulcers, resulting in a lifelong, progressively debilitating condition. The development of CVD is influenced by the condition of the veins and/or valves, ankle range of motion as part of the calf muscle pump, and the microcirculation.² The damage to the veins from injection drug use (IDU) continues to evolve even after IDU has stopped. In our work on injection drug users receiving methadone maintenance treatment, we found an 87% point prevalence of CVD, with 52% of affected persons having the most advanced stages of disease.³ Most damage appears to occur in persons who have injected in the groin, legs, and feet. In injection drug users, CVD occurs in middle-aged persons comparably younger than in the general population in which CVD occurs in the sixth or seventh decade. In a study of human immunodeficiency virus-positive persons, we found that injection drug users had less ankle plantar and dorsiflexion and inversion-eversion than those who did not inject drugs.⁴ A causal model supported the hypothesis of ankle mobility as a mediator of the effect of IDU on CVD. Significant impairment of quality of life occurred with leg pain causing increased functional impairment with worsening CVD; stair climbing and walking were

also adversely affected.⁵ Leg pain reduced effectiveness of the calf muscle pump function. Low income and educational levels were common in our samples and are associated with less access to care and issues of health literacy. We currently have funding to test specific hypotheses linking leg pain, pump function, and general mobility to CVD progression in 600 persons with a history of drug abuse. We encourage researchers and clinicians to consider the plethora of complications of drug use in addition to blood-borne pathogens as persons who injected drugs continue to age because these complications have an important impact on quality of life and are an economic burden.

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Prisoners (Should) Count

It is difficult to understand a survey of injection drug users¹ that ignores "institutionalized persons," including, specifically, prisoners. The comment of the author that the excluded individuals "represent less than 2% of the US population"^{1(p166)} gives scant comfort. The incarcerated population in the United States numbers more than 2.3 million persons,² and a significant proportion of the inmates are injection drug users.

What could be the reason for excluding a cohort that includes so many of the individuals whose characteristics are being studied—especially when those individuals are, very literally, a captive population?

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In reply

I thank Pieper and colleagues for sharing their insights on the problem with CVD among injection drug users and for reminding readers that the medical, social, and psychiatric