RESEARCH LETTER

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

Postoperative 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.1 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 recurrence; 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 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-
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-

<table>
<thead>
<tr>
<th>Patient No./ Sex/ Age, y</th>
<th>Disease Duration, y</th>
<th>Involved Intestine</th>
<th>Type of Surgery</th>
<th>Reason for Surgery</th>
<th>Previous Surgery</th>
<th>Current Smoking Status</th>
<th>Oral Contraceptives After Surgery</th>
<th>Medication Before Surgerya</th>
<th>Recurrence After Surgery at 2 y (Type of Recurrence)</th>
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</thead>
<tbody>
<tr>
<td>Infliximab + methotrexate groupb</td>
<td>1/M/64</td>
<td>ileocecal</td>
<td>ileocecal resection</td>
<td>Stricture</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>Mesalamine, prednisone cycles</td>
<td>No</td>
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<td>ileocecal resection</td>
<td>Stricture</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>Mesalamine, prednisone cycles</td>
<td>No</td>
<td></td>
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<tr>
<td>3/F/24</td>
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<td>ileocecal resection</td>
<td>Stricture</td>
<td>No</td>
<td>No</td>
<td>Never</td>
<td>Mesalamine, prednisone cycles</td>
<td>No</td>
<td></td>
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<tr>
<td>4/F/23</td>
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<td>ileocecal resection</td>
<td>Stricture</td>
<td>Yes</td>
<td>Yes, 5-6/d</td>
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<td>Mesalamine, prednisone cycles, azathioprine</td>
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<td>ileal resection</td>
<td>Stricture</td>
<td>Yes</td>
<td>Yes, 20/d</td>
<td>NA</td>
<td>Mesalamine</td>
<td>No</td>
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<td>Stricture</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<td>No</td>
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<td>No</td>
<td>No</td>
<td>NA</td>
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<td>NA</td>
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<td>No</td>
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<td>Mesalamine, prednisone cycles</td>
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<td>Mesalamine</td>
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<td>Mesalamine</td>
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<td>ileal resection</td>
<td>Stricture</td>
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<td>No</td>
<td>NA</td>
<td>Mesalamine, prednisone cycles</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

a The use of every medication was stopped at least 4 weeks before surgery.
b Infliximab, 5 mg/1 kg of body weight, was given with methotrexate, 10 mg/wk by mouth.
c The mesalamine dosage was 2.4 g/d.
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. 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 and further indicate that mesalamine is not an effective therapy to prevent recurrence.

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). 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]).

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 evidence 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 recurrence is warranted.
1. Armstrong GL. Injection drug users in the United States, 1979-2002: an ag-


4. Pieper BA, Templin T, Ebright JR. Ankle mobility in relation to chronic ve-
 nous insufficiency in HIV-Positive persons with and without a history of in-

5. Pieper B, Templin T. Lower extremities changes, pain, and function in injec-

Prisoners (Should) Count

It is difficult to understand a survey of injection drug users\(^1\) that ignores “institutionalized persons,” includ-
ing, specifically, prisoners. The comment of the author that the excluded individuals “represent less than
2% of the US population\(^{\text{1}(\text{pi}	ext{e}	ext{p}	ext{er} @
\text{w}	ext{a}	ext{y}	ext{e}	ext{n}.	ext{e}	ext{du}	ext{.}	ext{r}	ext{.e}	ext{.g}	ext{.u}	ext{t}	ext{.m}	ext{.e}	ext{.d}	ext{.a}	ext{.m}	ext{.e}	ext{.p}	ext{.i}	ext{.n}	ext{.s}	ext{.t}	ext{.e}	ext{.o}	ext{.f}	ext{.s}	ext{.c}	ext{.h}	ext{.e}	ext{.m}	ext{.a}	ext{.m}	ext{.e}	ext{.l}	ext{.m}	ext{.e}	ext{.d}	ext{.a}	ext{.y}.\text{u}	ext{.s}.	ext{e}	ext{.r}	ext{.s}	ext{.}\text{f}	ext{.o}	ext{.r}	ext{.s}	ext{.t}	ext{.e}	ext{.n}	ext{.o}	ext{.f}	ext{.a}	ext{.l}.
heads)" gives scant comfort. The incarcerated population in the United States numbers more than 2.3 million persons,\(^2\) and a significant pro-
portion of the inmates are injection drug users.

What could be the reason for excluding a cohort that in-
cludes so many of the individuals whose characteris-
tics are being studied—especially when those individu-
als are, very literally, a captive population?

Robert G. Newman, MD, MPH

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10019 (rnewman@icaat.org).


2. Harrison PM, Beck AJ. US Department of Justice, Bureau of Justice Statistics,

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

also adversely affected.\(^3\) Leg pain reduced effectiveness of
the calf muscle pump function. Low income and educa-
tional levels were common in our samples and are associ-
ated with less access to care and issues of health literacy.
We currently have funding to test specific hypotheses link-
ing 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 im-
port on quality of life and are an economic burden.

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Robert S. Kirsner, MD, PhD
Thomas N. Templin, PhD
Thomas J. Birk, PhD, MPT

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