Therapy of Metronidazole With Azathioprine to Prevent Postoperative Recurrence of Crohn's Disease: A Controlled Randomized Trial

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Background & Aims: **More than 80% of Crohn's disease (CD) patients undergoing resection suffer recurrence of their disease. Therapy with aminosalicylates, antimetabolites, or antibiotics leads to a modest reduction in the incidence of recurrence.** ***Goal:*** **We sought to examine whether metronidazole for 3 months together with azathioprine (AZA) for 12 months is superior to metronidazole alone to reduce recurrence of postoperative CD in "high-risk" patients.** ***Methods:*** **CD patients undergoing curative ileocecal resection with ≥1 risk factor for recurrence received metronidazole (3 months) and AZA/placebo (12 months). The primary end point was the proportion of patients with significant endoscopic recurrence 3 and 12 months after surgery. Secondary end points included clinical recurrence, safety, and tolerability of treatment.** ***Results:*** **Eighty-one patients were randomized; 19 discontinued the study early. Significant endoscopic recurrence was observed in 14 of 32 (43.7%) patients in the AZA group and in 20 of 29 (69.0%) patients in the placebo group at 12 months postsurgery ($P = .048$). Intention-to-treat analysis revealed endoscopic recurrence in 22 of 40 (55%) in the AZA group and 32 of 41 (78%) in the placebo group at month 12 ($P = .035$). At month 12, 7 of 32 patients had no endoscopic lesions in the AZA group, versus 1 of 29 in the placebo group ($P = .037$).** ***Conclusions:*** **Despite the enhanced risk of recurrence, the overall incidence of significant recurrence was rather low, probably owing to the metronidazole treatment that all patients received. Concomitant AZA resulted in lower endoscopic recurrence rates and less severe recurrences 12 months postsurgery, predicting a more favorable clinical outcome. This combined treatment seems to be recommendable to all operated CD patients with an enhanced risk for recurrence.**

The majority of patients with ileocecal Crohn's disease (CD) who undergo surgical resection develop postoperative recurrence of the disease in the neoterminal ileum.[1–3] Seventy-three percent of all operated patients have endoscopic signs of recurrent disease 1 year after surgery, and 85% have recurrence after 3 years.[4] Moreover, the severity of the endoscopic lesions has been predictive of the further clinical course of the disease. None of the currently available medical therapies have influenced the incidence of postoperative recurrence to an important extent. Studies with mesalamine preparations have yielded conflicting results. The benefit of continuous treatment with rather high doses of these drugs was at most only modest.[5]

An alternative treatment is the immunomodulator 6-mercaptopurine (6-MP), although the results are not all that convincing. Whereas in a prospective trial a fixed dose of 6-MP of 50 mg/d was significantly better in preventing endoscopic recurrence 1 and 2 years postoperatively[6] in comparison with 3 g of a sustained-release formulation of mesalamine (Pentasa, Ferring, Denmark) or placebo, no difference between AZA and mesalamine was seen in prevention of clinical recurrence in another study.[7]

Furthermore, antibacterial agents directed against anaerobic bacteria (ornidazole and metronidazole) were shown to be effective in reducing the severity of endoscopic recurrence, but prolonged administration of these antibiotics caused significant toxicity, mainly neuropathy and gastrointestinal intolerance.[8,9] The role of intestinal bacteria as inducers of recurrent CD has recently received a lot of interest, because reinfusion experiments showed that signs of inflammation appear within 8 days after the contact between the ileal mucosa and the ileal fluid has been restored, except when this fluid has been sterilized.[10–12]

It was the goal of the present study to compare the theoretically most potent prevention strategy, a combination of the immunomodulator azathioprine (AZA) and a 3-month course of metronidazole, to the latter treatment alone in patients carrying an elevated risk of developing postoperative recurrence of CD.

Abbreviations used in this paper: AZA, azathioprine; 6-MP, 6-mercaptopurine; CD, Crohn's disease; CDAI, Crohn's disease activity index.

0016-5085/08/$34.00
doi:10.1053/j.gastro.2008.07.010

Methods

Patients

All consecutive patients undergoing curative ileal or ileocolonic resection with ileocolonic anastomosis for CD at 2 teaching hospitals (University Hospital Leuven and Imelda General Hospital, Bonheiden, Belgium) between August 1999 and September 2005 were invited to participate in the trial. A requirement for eligibility was the presence of ≥1 risk factor for the development of early/severe postoperative recurrence of their CD, based on the available literature: young age (<30 years); active smoking; corticosteroid use in the 3 months before surgery; surgery for the 2nd, 3rd, or 4th resection; and perforating disease, namely, abscess or fistula as an indication for surgery.[13–15]

Patients had to be between 18 and 70 years old and had to understand and sign a written informed consent form. Women of childbearing age needed to have a negative pregnancy test and had to use adequate birth control measures during the whole study.

Exclusion criteria included the presence of macroscopic evidence for CD proximally or distally to the site of resection or the presence of frank pancolitis or an ileorectal anastomosis (ileosigmoidal anastomosis was allowed). Patients with a stoma were also excluded, as well as those who were operated on for fibrostenosis only, without evidence of inflammatory activity on histology. Patients with former intolerance to metronidazole and/or AZA, who wished to become pregnant during the study, who had a low white blood cell count at inclusion (<4000), who had alcohol or drug abuse, or who had used AZA in the 2 months before surgery were also excluded, as well as patients with malignancies and/or ongoing infectious disease (hepatitis, tuberculosis, AIDS) with the exception of herpes simplex infection. Former use of biologicals was not permitted. The trial was approved by the medical ethical committee at the University of Leuven, Belgium.

Treatment

All patients received 3 months of metronidazole therapy at a dose of 250 mg 3 times per day. Patients who could not tolerate metronidazole were switched to ornidazole 500 mg twice per day orally. Half of the patients also received AZA; the other half received placebo. The dose of AZA was body weight dependent. Patients whose body weight was <60 kg received 2 tablets of AZA (100 mg) or placebo, whereas patients weighing >60 kg received 3 tablets or 150 mg AZA. Hence, the number of tablets sometimes changed during the study. Randomization took place in the pharmacy of the Leuven University Hospitals within 2 weeks after surgery. The random allocation sequence was delivered by a randomization program written in Visual Basic version 6. In principle, patients started their medication as soon as they were able to resume oral intake.

At the time of surgery, all concomitant anti-inflammatory medications were discontinued, except for glucocorticosteroids, which were gradually tapered over 6 weeks after surgery. Antibiotics were allowed during the study for concurrent infections, but not for CD. Topical therapy for perianal CD could be continued if necessary. Cholestyramine was allowed for the treatment of bile acid diarrhea. Patients were instructed to take their other drugs at least 1 hour after the intake of cholestyramine.

Study Procedures

Patients underwent clinical evaluation with physical examination and biochemical analysis at baseline and weeks 2, 6, 12, 20, 28, 36, 44, and 52 after randomization. Laboratory assessments included peripheral blood counts, C-reactive protein levels, alkaline phosphatase, bilirubin, serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, creatinine, and urea levels. At week 12 and 52, an ileocolonoscopy was performed with determination of Rutgeerts' score for ileal recurrence of CD by an endoscopist who was unaware of treatment assignment (Table 1).[4] Adverse events and concomitant medication were recorded at every scheduled or unscheduled visit. Adverse events were recorded as mild, moderate, severe, or life threatening and the relationship with the study drugs was assessed as not related, possibly related, probably related, or definitely related. All events were followed to satisfactory resolution and/or stabilization. All actions taken were recorded in the files.

Elevations of liver function tests, regularly observed with metronidazole and also with AZA, were dealt with as follows: An elevation of transaminases up to 3 times the upper limit of normal and of alkaline phosphatase 2 times the upper limit of normal were allowed and did not lead to a change in therapy or discontinuation. More severe abnormalities led to discontinuation of therapy and study participation. Leukopenia, a common, dose-dependent side effect of AZA, was handled as follows: If the total white count was <3500, the dose of AZA/placebo was reduced to 1 tablet (50 mg) per day. If on 1

Table 1. Rutgeerts' Endoscopic Score for Recurrence of CD in the Neoterminal Ileum

Score	Criteria
0	No lesions
1	<5 Aphthoid ulcers
2	>5 Aphthoid ulcers with normal mucosa in between or skip areas of larger lesions *or* lesions confined to the ileocolonic anastomosis
3	Diffuse ileitis with larger ulcers but normal mucosa in between
4	Diffuse ileitis with large ulcers, nodules/narrowing without normal mucosa in between