Low-Dose Maintenance Therapy With Infliximab Prevents Postsurgical Recurrence of Crohn’s Disease

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This article has an accompanying continuing medical education activity on page e79. Learning Objectives—At the end of this activity, the learner should be able to understand the role of infliximab in the prevention of postsurgical Crohn’s disease.

See Editorial on page 556.

BACKGROUND & AIMS: Infliximab might prevent postsurgical recurrence of Crohn’s disease. However, it is unclear whether long-term therapy is necessary and whether alternative strategies could be applied to minimize potential side effects and reduce the costs of treatment. METHODS: We performed a prospective cohort study in 12 consecutive patients, treated immediately after surgery with maintenance infliximab (5 mg/kg), who did not have clinical or endoscopic evidence of disease recurrence after 24 months; they were followed up for an additional year. Infliximab treatment was then discontinued; patients with disease recurrence, based on endoscopy (Rutgeerts score, ≥2), were given lower doses of infliximab (starting with 1 mg/kg) to re-establish mucosal integrity. Surrogate markers of disease activity (fecal calprotectin [FC], C-reactive protein, and erythrocyte sedimentation rate) were assessed after each infliximab dose. RESULTS: None of the patients had clinical or endoscopic recurrence of Crohn’s disease 3 years after surgery. However, discontinuation of infliximab caused endoscopic recurrence after 4 months in 10 of 12 patients (83%). All 10 patients then were treated again with infliximab, which, at a dose of 3 mg/kg every 8 weeks, restored and maintained mucosal integrity for 1 year. Among the surrogate markers, FC levels correlated with endoscopic scores (Wald test, \( P < .0001 \)).

CONCLUSIONS: Long-term maintenance therapy with infliximab is required to maintain mucosal integrity in patients after surgery for Crohn’s disease. However, a dose of 3 mg/kg (a 40% reduction from the standard dose) was sufficient to avoid disease recurrence, determined by endoscopy, in all patients at 1 year. FC levels correlate with mucosal status at different infliximab doses.

Keywords: Crohn’s Disease; Postoperative Recurrence; Prevention; Infliximab.

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By contrast, infliximab, a monoclonal antibody anti–tumor necrosis factor (TNF)-α, has shown a remarkable efficacy in preventing this complication. We first reported in 2006 a case treated with infliximab intravenously immediately after surgery to prevent recurrence of colonic Crohn’s disease who had been disease free for 48 months after surgery.‡ This study subsequently was expanded to include a total of 7 patients similarly treated and compared with a control group given mesalamine 2.4 g/d. That study showed at 2 years the complete absence of endoscopic and clinical recurrence in all infliximab-treated patients as opposed to a combined clinical/endoscopic recurrence rate of 75% in mesalamine-treated controls.§ More recently, Regueiro et al¶ confirmed these findings in a small randomized controlled trial that included 11 infliximab-treated patients and 13 placebo-treated controls: endoscopic recurrence at 1 year was prevented in 91% of infliximab-treated patients versus 15% of controls. Although these data may benefit from confirmation by a large trial, they uniformly show that therapy with this biologic—initiated immediately after surgery—prevents endoscopic and clinical recurrence of disease in the large majority of patients.

However, current studies do not answer a few additional important questions. First: is infliximab still effective in preventing recurrence in the long term? Second: if so, for how long should the drug be continued? Can it be stopped while still maintaining the patient in full endoscopic and clinical remission? If not, can we minimize risks linked to potential long-term side effects and at the same time reduce the costs of treatment?

To provide an answer to these questions we followed up a total of 12 patients in the current study treated within 2 weeks of surgery with infliximab at standard induction and maintenance doses, who were free of clinical and endoscopic recurrence at 24 months, for a total of 3 years. Subsequently, after stopping the medication, which resulted in endoscopic recurrence at 24 months, for a total of 3 years. Subsequently, after stopping the medication, which resulted in endoscopic recurrence at 24 months, for a total of 3 years. Subsequently, after stopping the medication, which resulted in endoscopic recurrence in the majority of patients, we explored the possibility of
re-establishing and maintaining mucosal integrity with lower doses of infliximab, a potentially effective strategy to minimize long-term risks and reducing costs. As a secondary objective of this study we also sought a correlation between surrogate markers of intestinal inflammation (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], and fecal calprotectin [FC]) and infliximab doses and endoscopic appearance.

**Patients and Methods**

We enrolled in the current study a total of 12 consecutive patients treated postoperatively with infliximab and free of clinical and endoscopic recurrence at 2 years. The clinical features of all 12 patients are outlined in Table 1. The age ranged from 23 to 64 years (median, 38 y). Six of these patients had an ileocecal resection (during which a fistula tract was removed in 3 of the patients), 2 patients had a segmental ileal resection (the patients previously had been subjected to ileocecal resection), 2 patients had a segmental sigmoid resection (1 of these patients previously had been subjected to ileocecal resection), and 2 patients had a right hemicolectomy with ileal resection (1 patient had a fistula tract removed during resection and both patients had an abscess drained several weeks before surgery). Indications for resection included activity with aggressive disease (3 patients) or stricturing disease (7 patients), the latter associated in 2 cases with disease activity.

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<tr>
<th>Patient no.</th>
<th>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>Medication before surgery</th>
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<td>Mesalamine, prednisone cycles, 6-mercaptopurine</td>
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</table>

*Every medication was stopped at least 4 weeks before surgery.*

Table 1. Crohn’s Disease Patients Treated With Infliximab After Surgery Without Recurrence at 2 Years

The clinical recurrence grading scale (1, absent; 2, mild; 3, moderate; 4, severe symptoms) proposed by Hanauer et al was used in this report. Lack of clinical recurrence was defined as a score of less than 2 on the Rutgeerts scale. When present, mucosal lesions limited to the surgical anastomosis were not considered in the scoring process. These patients were followed up for an addi-
tional year under the same conditions and, if still free of clinical and endoscopic recurrence, were enrolled in the dose-finding study.

The design of the dose-finding study is illustrated in Figure 1. Briefly, at 3 years, in all patients free of recurrence, infliximab was stopped and colonoscopy was performed after 16 weeks (ie, after skipping one infusion and immediately before the following scheduled infusion administered every 8 weeks). During colonoscopy we took great care each time to rinse the perianastomotic zone extensively with water and film it. We chose an early rather than a standard (6–12 mo) time for a check-up endoscopy because postsurgical recurrence, if present, has been shown to start immediately after surgery.11 If negative for mucosal lesions 16 weeks after stopping therapy, the patients were subjected only to follow-up evaluation without any additional treatment (a colonoscopy was performed after 1 additional year). If positive for mucosal lesions (Rutgeerts score, ≥2) the patients were given infliximab within days at the next preplanned infusion date at a dose of 1 mg/kg bw. After 3 infusions at the new dosage, at week 4 of the following 8-week dosing interval, they again were checked for mucosal healing. If mucosal damage still was present then the infliximab dose was increased, administered at the preplanned infusion date, and its effect on mucosal integrity was checked again as described earlier. When mucosal healing was reached (score, <2) in all patients, a confirmatory colonoscopy was performed after 4 additional infusions, 4 weeks after the last dose, with the patients still being treated with the apparently effective drug dose. Surrogate markers of disease activity (FC, CRP, and ESR) always were tested before colonoscopy and after at least one additional infliximab infusion at any given dose (at midinterval).

Before colonoscopy the markers were determined 3 days before the procedure, just before starting preparation (because it cannot be excluded that bowel preparation per se may increase FC levels).12,13

Subsequently, we sought a correlation between these markers and both infliximab dose and endoscopic scores (see the Statistical Methods section). In addition, the patients were subjected to scheduled physical examination/interviews together with a battery of routine blood tests (complete blood count, albumin, liver and renal function tests, electrolytes, autoantibodies) every 3 months. Patients were blinded with regard to the medication dose being administered at any given time. Likewise, scoring of endoscopic lesions was performed by reviewing the film of the colonoscopy the day after the examination by an independent investigator who was unaware of the patient’s name and current dose of infliximab. The study protocol was approved by the institution’s ethics committee. The study design was explained clearly to the patients in detail, including the possibility of undergoing several colonoscopies as well as the potential gain from a reduction in drug dosage in their long-term treatment. All patients signed an informed consent form.

**Statistical Methods**

For patients enrolled in the infliximab dose-titration study, a t test was used to compare mean levels of CRP, ESR, and FC observed before and after stopping the medication. Median differences between pairs of endoscopic scores at different infliximab doses were tested by using a Wilcoxon signed-rank test and P values were adjusted successively for multiple testing using Holm’s procedure. In addition, we performed a median regression analysis to assess nonparametrically the association between endoscopic scores and FC. A Wald test was used to test the null hypothesis that a log-linear model with constant intercept was adequate relative to a first-degree polynomial model. Similarly, a linear model with constant intercept was tested against a second-degree polynomial when regressing FC, CRP, and ESR on different infliximab doses. In all cases, the significance level was set at 5%.

**Results**

A total of 12 patients treated immediately postoperatively with infliximab 5 mg/kg bw on a maintenance basis and free of clinical and endoscopic recurrence at 2 years were given infliximab for another year at the same dose and colonoscopy was performed immediately thereafter. None of the patients had mucosal or clinical recurrence as defined in the Patients and Methods section, and none of them reported serious side effects. We only recorded mild, single, short-lived, self-limiting episodes of abdominal pain in 3 patients that were attributed to a typical food-borne infection. Three additional patients reported a flu-like syndrome with a possible tracheitis/bronchitis (but a negative chest radiograph, which was recommended only for precaution), which lasted more than 1 week and was treated with over-the-counter medications. Finally, 1 patient presented with a possible herpes zoster infection in his upper trunk that we could not examine (because the patient is living in another city). By the time he was seen by the local dermatologist the lesion apparently had disappeared and he was not treated with antiviral medications. No blood test abnormalities were detected during the period of study except, as already reported in 2 patients in our previous study, for transient and borderline positivity for lupus anticoagulants in 2 additional patients without any of the typical features of frank systemic lupus erythematosus. Thus, these results confirmed the remarkable efficacy of infliximab in preventing postsurgical recurrence of Crohn’s disease even in the long term.

**Figure 1.** Design of the dose-finding study. The initial low dose of infliximab was 1 mg/kg bw. IFX, infliximab; MH, mucosal healing.
Next, the medication was stopped in all patients. They were checked carefully for symptomatic recurrence of disease, and a colonoscopy was performed after 16 weeks. The results are summarized in Table 2. Two of the 12 patients had no endoscopic recurrence upon stopping infliximab and were not treated further. After 16 and 20 months of follow-up evaluation they remain completely disease-free (they had an additional colonoscopy performed after 12 months). By contrast, 10 of 12 patients had an endoscopic recurrence defined as a Rutgeerts score of 2 or greater. Of these patients, 8 patients had a score of 3. By contrast, with the typical appearance of the mucosa after postsurgical recurrence (upon which the Rutgeerts score is based), ulcerative lesions tended to be confluent and superficial, with ill-defined margins. An example of such patients is given in Supplementary Figure 1, which compares the status of the mucosa 3 years after surgery under maintenance 5 mg/kg bw infliximab treatment (Supplementary Figure 1A) with its appearance 16 weeks after stopping the medication (Supplementary Figure 1B). CRP and FC levels increased in all patients compared with their previous levels (mean ± SD, 410 ± 60 vs 40 ± 15 mg/kg for FC; normal range, 0–50 mg/kg; and 12.5 ± 4 vs 3.0 ± 1.4 mg/L for CRP; normal range, 0–5 mg/L; P < .001 for both). ESR also increased compared with the baseline level but remained within the normal range (14 ± 8 vs 9 ± 5 mm/h; normal range, 0–20 mm/h; P = NS). None of the patients was symptomatic at the time of colonoscopy.

The 10 patients with endoscopic lesions after interruption of therapy then were administered low doses of infliximab as detailed in the Patients and Methods section.

We elected to treat these patients initially with the lowest dose (1 mg/kg bw) to allow for subsequent dose escalation if necessary. The data, detailed in Table 2, show that such a dose was not effective in any of the patients to re-establish mucosal integrity after 3 infusions (as determined by endoscopic recurrence scores at the midinterval). Indeed, the scores remained identical to baseline (ie, after stopping infliximab). Infliximab dose then was increased to 2 mg/kg bw in all patients. Four weeks after the last of 3 infusions at a 2-mg/kg bw dose a new colonoscopy was performed. As illustrated in Table 2, doubling the infliximab dose improved the endoscopic score in most patients (P = .006). However, the score did not decrease to less than 2 in 8 of 10 patients, thus indicating that such a dose still was insufficient in the large majority of patients to re-establish mucosal integrity. Although the 2 patients with a score of 1 were informed that, by contrast with most patients, they essentially had reached endoscopic healing at the dose of 2 mg/kg bw, they elected to continue the study (unblinded) at the higher dose. This time, the dose was increased to 3 mg/kg bw and, again, a colonoscopy was performed as described earlier. Such a dose further reduced the endoscopic score (P = .007) and was sufficient in all patients to re-establish mucosal integrity. None of the patients had a score greater than 1, and 4 patients had a score of 0. At this time, all patients were kept on infliximab maintenance therapy at 3 mg/kg bw and asked to repeat the colonoscopy after 4 additional infusions (ie, after approximately 1 full year at a dose of 3 mg/kg bw). The final colonoscopy confirmed mucosal healing in all patients with further improvement (from 1 to 0) in 1 patient. The data related to the dose-finding study are synthesized and represented graphically in Figure 2. The mucosal appearance of the neoterminal ileum in a typical patient (patient 11) treated with different infliximab doses is illustrated in Figure 3.

During the study, in addition to the scheduled physical examinations and blood tests as detailed in the Patients and Methods section, we also determined FC, CRP, and ESR 3 days before colonoscopy (before initiating bowel preparation) and after at least one additional infliximab infusion at any given dose (at midinterval). As illustrated in Figure 4A and B we found a statistically significant, negative association between infliximab dose and FC and between infliximab dose and CRP (P < .0001 for both). However, in the latter case, CRP decreased for the first 1-mg/kg bw dose increase and it remained constant for subsequent dose increases. By contrast, the median ESR was approximately constant for all infliximab dose levels (Figure 4C; P = .14). In addition, there was a statistically significant, positive association between the median FC determined immediately after stopping infliximab and the median ESR determined 3 days after stopping infliximab (Table 2, Figure 4D).

### Table 2. Response to Treatment After Long-Term Infliximab Administration and Dose Reduction

<table>
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<th>Patient no.</th>
<th>Endoscopic or clinical recurrence after surgery (at 3 years)a</th>
<th>Endoscopic score after 3 infusions of infliximab</th>
<th>Endoscopic score after 3 infusions of infliximab</th>
<th>Endoscopic score after 3 infusions of infliximab</th>
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<td>1.8 ± 0.4</td>
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aInfliximab, at 5 mg/kg bw, was given as induction (2, 4, and 6 wk) and maintenance therapy (on an 8-week dosing interval).

bPatients with mucosal integrity after suspension of infliximab were excluded from the dose-titration study.

cDoes not include the patients without recurrence.
ately before colonoscopy and endoscopic scores (Figure 5). The rate of change of the median natural logarithm-FC for one unit change in endoscopic scores was equal to 0.84 ($P < .0001$). That is, for every one unit change in endoscopic scores, the ratio between 2 successive median FC values was constant and equal to 2.31 (95% confidence interval, 2.08–2.61).

All along the titration study the patients reported subjective well-being without any symptoms suggesting clinical recurrence of the disease. Again, 2 patients reported a flu-like syndrome that was self-limited and treated with over-the-counter medications. Although we did not formally study it, quality of life was reported as unaltered/good during the study by all patients and 5 of 12 referred to being in a better mood and having more energy to perform everyday tasks.

Discussion

Prevention of postsurgical recurrence of Crohn’s disease is a fundamental task in the practical management of patients with this condition. Indeed, as of today, the large majority of affected individuals will undergo surgery within a few years of diagnosis. After surgery, the disease tends to occur in a similar fashion and usually within a short time. If left untreated, approximately 80% of patients will have an endoscopic recurrence within 1 year from surgery, and in a large majority of them the disease will manifest clinically within a variable period of time (reviewed by Sandborn and Feagan). Until recently, such a complication appeared almost unavoidable because the most effective medication tested—azathioprine/6-mercaptopurine—only reduces recurrence, at best, by approximately 25% and is associated with a high rate of adverse events. Infliximab, a monoclonal anti–TNF-α antibody effective in inducing remission in the naturally occurring disease, has shown a remarkable efficacy in preventing postsurgical recurrence since 2006. The data stem from a report and a series from our center as well as from a small recent randomized controlled trial. Globally, these data indicate that infliximab

Figure 2. Postsurgery endoscopic score versus infliximab dose. The graph illustrates the endoscopic scores at each infliximab dose in the 10 patients presenting with postsurgical recurrence (score, ≥2) 16 weeks after stopping therapy. Individual data points are plotted as sunflowers with multiple petals. The boxes (dotted line) are centered on the mean (solid line) of the scores observed at different infliximab doses, with total height equal to twice the standard deviation. The statistical significance ($P$) for the median difference between pairs of endoscopic scores at different drug doses also is reported. IFX, infliximab; q8wk, 8-week dosing interval.

Figure 3. Appearance of the mucosal anastomosis at different infliximab doses: (A) 5 mg/kg bw on an 8-week dosing interval for 3 years after surgery; (B) 1 mg/kg bw, 4 weeks after 3 infusions on an 8-week dosing interval; (C) 2 mg/kg bw, 4 weeks after 3 infusions on an 8-week dosing interval; (D) 3 mg/kg bw, 4 weeks after 3 infusions on an 8-week dosing interval; and (E) 3 mg/kg bw on an 8-week dosing interval for 1 year. The progressive increase in infliximab dose re-established mucosal integrity, which was maintained at 1 year.
given immediately after surgery may prevent recurrence in 90% to 100% of patients. Given the strength of the data and the agreement among these studies it appears that a larger trial, however needed, may merely confirm these observations. One of the essential issues that remain to be addressed in this context is whether infliximab could be stopped in the long term and whether alternative strategies may be as effective as the standard maintenance treatment to preserve mucosal integrity. This issue needs to be addressed for several reasons. First, it is possible that some of the patients treated immediately after surgery may have never developed the disease. Indeed, approximately 20% to 30% of patients do not present with endoscopic recurrence after 1 year, and likely never will during their lifetime. Second, although infliximab has been proven safe over the years concerns still remain regarding long-term side effects, especially with regard to development of solid and hematologic malignancies in young adults. Such side effects may be related directly to the dose and time of exposure to the medication as well as to the concomitant use of immunosuppressives. Finally, infliximab costs still represent a significant deterrent for its uninterrupted use in the long term.

In this study, after evaluation of the long-term benefit of infliximab maintenance treatment in preventing recurrence, we studied whether its suspension causes endoscopic recurrence and whether, in such cases, a lower dose of medication may be sufficient to re-establish mucosal integrity. The objective of the study was to achieve mucosal healing in such patients with the lowest effective dose of infliximab. Indeed, the minimal dose of infliximab currently used in gastroenterology, 5 mg/kg bw, to treat both Crohn’s disease and ulcerative colitis has not been determined by any trial designed for the purpose. Although an increase in dosage or a shortening of the dosing interval often is advocated in patients with a decreased response to the standard regimen, little is known about the lower limit of the therapeutic window of this medication in these conditions. In rheumatology, some, although not all, studies already have shown that treating patients with both rheumatoid arthritis and ankylosing spondylitis with lower-than-standard doses of infliximab may be an effective strategy to maintain remission while potentially minimizing risks and reducing costs.

To this aim we followed up a group of patients treated for a total of 3 years after surgery with infliximab at standard 5-mg/kg bw doses. None of these patients had endoscopic and/or clinical recurrence at 3 years. Infliximab then was suspended in all patients. Endoscopic re-evaluation 16 weeks after...
stopping the medication showed clear endoscopic signs of recurrence in 10 of 12 patients (83%; Rutgeerts score of 3 in 8 patients). Such a result was consistent with well-known recurrence rates, in the absence of medications, reported in the literature and provided additional evidence of the remarkable efficacy of infliximab in preventing recurrence. However, it also showed that the medication should be continued beyond 3 years to maintain its benefit.

We then elected to restart infliximab at low doses (beginning with 1 mg/kg bw), leaving dosing intervals unaltered. Each tested dose of infliximab was administered over 3 infusions and its effect was checked by colonoscopy at mid interval. If negative for mucosal healing the dose of the medication was increased gradually, starting from the next scheduled infusion.

The results show that although doses of 1 and 2 mg/kg bw of infliximab were insufficient in the majority of patients to achieve mucosal healing, increasing the dose to 3 mg/kg bw re-established mucosal integrity in all treated patients. Mucosal healing in patients given the 3-mg/kg dose was checked and confirmed after 1 full year of treatment. No important side effects or symptomatic recurrence of the disease was observed in any patient during the entire duration of the dose-finding study.

Thus, we report here that lower-than-standard doses of infliximab may be effective in maintaining Crohn’s disease in full remission, at least in patients who have undergone surgery. Whether low doses of infliximab may be effective in any circumstances in maintaining remission in the spontaneous disease is not clarified by our data. One could speculate that in the postsurgical setting Crohn’s disease may be much more responsive to medical therapy because of the relatively short natural history and the absence of complications. In addition, early phases of disease may be driven by cytokines (eg, TNF-α) different from those of late phases (reviewed by Peyrin-Biroulet et al).

Our study does not clarify whether treatment with more than 3 infusions at the lower doses of infliximab (1 and 2 mg/kg bw) would have shown efficacy in restoring mucosal integrity. For the drug to be considered effective in the spontaneous disease response should occur within 2 infusions. Also, we cannot exclude that an untested intermediate dose of infliximab (2.5 mg/kg bw) could have been sufficient to achieve mucosal healing. The obvious limitation in testing more doses and strategies in this study was the willingness of the patients to undergo colonoscopy every few months.

An additional interesting observation of our study, which could simplify the design of future trials, is the strong correlation between FC levels and mucosal status at the different doses of infliximab (Figures 4A and 5). Although it is known that this marker closely reflects inflammation of the intestinal mucosa in inflammatory bowel disease patients, it has not been used to test the effectiveness of therapy to prevent postsurgical recurrence of Crohn’s disease. In this study, FC levels appeared inversely correlated to infliximab doses and mucosal status and, in addition, to change very rapidly in response to infliximab infusion during the 8-week dosing interval (data not shown). By inference, these data suggest that in this context mucosal integrity during infliximab treatment may be the result of a fine continuous balance between the production of proinflammatory factors and tissue drug levels. ESR did not appear to correlate as well as FC with infliximab doses. CRP accuracy in predicting mucosal inflammation, in keeping with previous data, fell somewhat in between the other 2 markers.

Some potential limitations of our study should be discussed. First, the infliximab-treated patients enrolled in this investigation had not been compared in our initial study with a placebo-controlled group. However, that study did include 16 controls treated with standard doses of mesalamine, a medication reported in the largest meta-analysis to give a benefit of 13% over placebo in the setting of postoperative prevention of Crohn’s disease. Our current study had a long follow-up period (3 years), during which none of the infliximab-treated patients developed endoscopic recurrence. A recent meta-analysis of the relative literature indicated that the placebo effect, as expected, rapidly fades with time and that endoscopic recurrence rates in placebo-treated patients after 1 year are up to 80%. Indeed, Regueiro et al reported an 85% endoscopic recurrence rate after 1 year in placebo-treated patients as opposed to 9% in infliximab-treated patients, a result virtually superimposable to ours.

The current study also is lacking a placebo arm and therefore in theory the benefit of infliximab at low doses also could be the result of a placebo effect. However, all patients were followed up for a full year after initiating treatment with the potentially minimally effective dose (3 mg/kg bw). More importantly, patients were blinded with regard to the dose being administered, and a hypothetical placebo effect in the current study could not explain why mucosal lesions were more pronounced at the lower infliximab doses and why the latter strongly correlated with FC and CRP levels. Indeed, in this study each subject acted as his own control, a strategy that provides important evidence that the observed effects were the results of therapy. In addition, scoring of endoscopic lesions was performed by an independent endoscopist who was unaware of the patient’s name and current dose of infliximab and hence did not know when the patient had been enrolled (and the dose the patient was taking) or the preliminary results of the study up to that point (see the Patients and Methods section for more detail). Including a placebo arm in this follow-up study for its duration (2 years) would have been unethical, having clearly shown that stopping the medication does cause recurrence in the large majority of patients.

Another potential limitation of our study comes from the observation that postoperative endoscopic lesions may regress spontaneously with time and may not evolve. However, such an event is mostly limited to minor ileal lesions or to anastomotic lesions which probably do not represent true disease recurrence. Such lesions were not considered in the scoring process in this study. The close inverse relationship of the observed mucosal lesions with the blinded therapy regimens does indicate, again, that the drug effect was real.

Among our patients, 2 (patients 3 and 4) had a purely colonic disease. We realize that it is not very common to include such patients in postoperative prevention trials. Although there is a scarcity of specific studies of the disease in such settings, recurrence does occur after resection of the colon. Indeed, our patients had mucosal recurrence similar to the other patients when therapy was suspended.

An additional issue could be related to the inclusion in the study of 2 patients who had been treated with infliximab on demand before surgery. In both cases the patients had been managed before surgery in centers different from ours. They were not considered infliximab failures because they had never
been subjected to standard maintenance therapy. More importantly, in these 2 patients the medication had been administered at an advanced stage of disease, in the presence of strictures, and responded very little to medical therapy. Thus, our study did not clarify whether true primary anti-TNF nonresponders may respond less than others to infliximab after surgery. Similar considerations may apply to the postoperative prevention trial of Regueiro et al, which did include a sizeable proportion of patients treated with anti-TNF before surgery, patients who responded as well as the others.

A final point regards the relatively small number of patients enrolled in this study. We are aware that confirmation of our data by a larger, multicenter trial would be desirable. A large-scale dose-finding study may be difficult to perform because of potential problems with patient compliance with the scheduled procedures. In the current study we took time and great care to inform and continuously motivate our patients, and indeed none of them dropped out.

In conclusion, we have shown that infliximab administration immediately after surgery effectively prevents clinical and endoscopic recurrence at 3 years. Suspension of the medication causes endoscopic recurrence in a short time in the large majority of patients, thus indicating the need for uninterrupted therapy. In this group of patients an infliximab dose of 3 mg/kg bw (a reduction of 40% of the standard dose) was sufficient to re-establish and preserve mucosal integrity for 1 year in all patients. Lowering the dose of infliximab is potentially safer and is more cost effective than standard strategies and should be considered in the long-term management of patients undergoing treatment for prevention of postsurgical recurrence of Crohn’s disease. FC appeared to be an accurate surrogate marker of mucosal integrity in response to different doses of infliximab.

The findings of this study, if confirmed by larger trials, may bear implications for drug safety and pharmacoeconomics of biologics as well as for the global management strategy of Crohn’s disease patients who undergo surgery.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at doi:10.1016/j.cgh.2010.01.016.

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Conflicts of interest
The authors disclose the following: Dario Sorrentino has acted as a consultant and received fees from Schering-Plough, Centocor, and Abbott (study participants were informed about the potential conflicts of interest). The remaining authors disclose no conflicts. This study was not supported by the pharmaceutical industry.
Supplementary Figure 1. Appearance of the mucosal anastomosis during infliximab treatment and after its suspension. (A) The patient had been treated for 3 years after surgery with infliximab 5 mg/kg bw. (B) The same patient 16 weeks after interruption of infliximab therapy.