Crohn’s disease patients often suffer recurrence after surgery in a relatively short time. Hence, prevention of such complication is an important management consideration. Conventional medical therapies such as antibiotics, mesalamine, and thiopurines have shown little if any benefit for this indication. Recent promising data have shown that postoperative recurrence can be prevented in between 90 and 100% of patients when anti-tumor necrosis factor (TNF) are given immediately after surgery. Ongoing randomized clinical trials are now seeking to confirm these findings on a larger scale. This review will focus on the published studies that have used anti-TNFs to prevent postoperative recurrence, outline possible long-term strategies for these patients and review the potential implications of these data.

INTRODUCTION

There are unmet needs for therapy in Crohn’s disease (CD) (1) and this is particularly true for its complications. One of the most feared and yet frequent is recurrence after surgery. Up to 70-90% of patients will develop mucosal damage at the surgical anastomosis or the neoterminal ileum within a year from surgery. Of these patients approximately 60-70% will become symptomatic within 2 years and a substantial fraction will require a further resection (2). Hence prevention of post operative recurrence becomes an important consideration in the general management.

Conventional medical therapies such as antibiotics, mesalamine and thiopurines have been extensively tested for this indication but with little success due to lack of efficacy or adverse side effects (2). Although good results have been reported with the combination metronidazole-azathioprine, the reported benefit over placebo in preventing endoscopic recurrence at one year is only approximately 25% (3).

By contrast, anti-tumor necrosis factor (TNF) have been proven extremely effective in the treatment of moderate to severe CD, since 1995 (4). Recent promising data has also been published on their use for prevention of recurrence. These initial studies have demonstrated that post operative recurrence can be prevented in 90-100% of patients treated immediately after surgery (5). RCTs are now seeking to confirm these findings on a larger scale. Extensive systematic...
reviews have been published on the general subject of CD recurrence after surgery (2,6). We will focus here on the studies that have used biologics for such indication. We will then outline a long term strategy in patients initially responding to anti-TNF therapy after surgery. Finally, the clinical impact and the relevance of this experience in understanding the pathogenesis of the disease will be addressed.

What Started it All

The first report investigating the use of infliximab in the post operative setting was published by our group in 2006, and described a young woman operated on for colonic CD and treated immediately after surgery with infliximab. She has been in endoscopic and clinical remission for more than 4 years after surgery as opposed to five controls treated with mesalamine who developed recurrence by year two (7).

In a subsequent small prospective pilot study infliximab combined with low dose oral methotrexate was given in a nonrandomized fashion to seven patients and compared to oral mesalamine given to 16 controls following ileocolonic resection for CD (8). All patients suspended prior therapy (which included mesalamine and/or immunosuppressives but no infliximab) for a minimum of 4 weeks before surgery. The median disease duration was 7 years. Two patients were smokers. Infliximab (5 mg/Kg) induction was started within two weeks from surgery followed by standard maintenance treatment (every 8 weeks) with low dose methotrexate (10 mg/week p.o.). The latter was used since the study was started at a time when it was common practice to add an immunomodulator to prevent the formation of antibodies anti infliximab (9), a strategy later proven unnecessary for patients on maintenance therapy (10). In the control group sixteen patients were treated postoperatively with mesalamine 800 mg tid. The median disease duration was 5.5 years. Four patients were smokers. All patients suspended therapy (which did not include infliximab) at least four weeks before surgery.

The main outcome of the study was clinical recurrence at two years while the secondary outcome was endoscopic recurrence at two years. Clinical recurrence was defined as a score of 2 or greater on the Rutgeerts scale (13).

None of the infliximab treated patients had endoscopic or clinical recurrence after 2 years. Only minor side effects were reported. In the mesalamine group only 25% (4/16) of patients were disease free 2 years after surgery. Of patients with recurrent disease 44% had endoscopic relapse while 31% had both endoscopic and clinical recurrence.

These results were confirmed in 2009 by a small RCT which evaluated 24 patients, blindly randomised to treatment with either infliximab 5mg/kg (11 patients) or placebo (13 patients) (14). Therapy was started 4 weeks after surgery and continued at 8 weekly intervals for 1 year. The major objective of this study was the endoscopic recurrence at 1 year. Secondary objectives were clinical recurrence at 1 year (defined according to a CDAI > 200) and histologic recurrence at 1 year. The two groups of patients were similar with regard to the main clinical features including disease duration, previous surgery and smoking habits. Use of immunosuppressors was permitted during the trial if these medications had been started before surgery and the dose was constant after surgery.

Twelve months postoperatively all patients underwent colonoscopy. Endoscopic recurrence was reported in 84.6% of placebo treated patients compared to only 9.1% in the infliximab treated patients. In addition, 38% of the placebo treated patients had clinical recurrence at one year compared to none in the infliximab treated group. Histological recurrence (defined by neutrophil infiltration in lamina propria and epithelium) was reported in 30% of infliximab treated patients (as well as in all the placebo treated patients with endoscopic recurrence) but the meaning of this histologic finding as a risk factor for clinical recurrence is however questionable (15). As in our study, infliximab was well tolerated with only minor side effects in the two groups. One infusion reaction was reported in the infliximab group.

Thus, a total of 47 patients of whom 18 treated with infliximab were included in these two studies. The number of patients may be considered relatively small but the results were strikingly similar for both studies and in sharp contrast with those obtained with conventional medications (16).

Additional evidence that infliximab is remarkably effective in preventing postoperative recurrence of CD comes from our follow-up study published in 2010 (17). Twelve patients (seven of whom originally enrolled
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Although the available evidence suggests that infliximab might prevent post-surgical recurrence of CD the risk of potential side effects and the costs of treatment may represent significant deterrents for its long term use.

To address these issues we performed a prospective cohort study in 12 consecutive patients, seven of whom had been enrolled in the original study that showed infliximab efficacy in preventing recurrence (see above) (17). All patients were treated immediately after surgery with induction then maintenance infliximab (5 mg/Kg every 8 weeks) for a total of three years. At that time none had developed clinical or endoscopic recurrence. In this study) were treated with infliximab for a total of 3 years. At that time colonoscopy revealed that none of them had developed endoscopic or clinical recurrence. Infliximab was then stopped for a total of 4 months - skipping one dose and performing colonoscopy immediately before the next scheduled infusion. Colonoscopy showed that 10 out of 12 patients (83%) had developed endoscopic recurrence. Thus, those patients would have developed recurrence if left untreated after surgery.

The benefit shown with infliximab appears, from preliminary studies, to result also from another anti-TNF, Adalimumab. Adalimumab was tested in a nonrandomized study of 20 patients (18) most of whom were at high risk for postoperative recurrence (60% smokers, 35% had previous surgery, and 65% had perforating disease). Twelve months after surgery, only two patients (10%) had endoscopic recurrence while none of them had clinical recurrence. Another preliminary study by De Cruz et al. also confirms the efficacy of Adalimumab (19).

Long Term management: The Low Dose Option

Although the available evidence suggests that infliximab might prevent post-surgical recurrence of CD the risk of potential side effects and the costs of treatment may represent significant deterrents for its long term use.

In an attempt to address these issues we performed a prospective cohort study in 12 consecutive patients, seven of whom had been enrolled in the original study that showed infliximab efficacy in preventing recurrence (see above) (17). All patients were treated immediately after surgery with induction then maintenance infliximab (5 mg/Kg every 8 weeks) for a total of three years. At that time none had developed clinical or endoscopic recurrence. Infliximab was then stopped for 4 months and patients underwent colonoscopy. The latter showed recurrence in 10/12 patients. In these 10 patients infliximab therapy was re-initiated with lower doses (starting with 1 mg/Kg) with the primary objective of re-establishing mucosal integrity. The dose of infliximab could be increased until mucosal healing was reached and then maintained, at that potentially effective dose, for at least one year. Low anti-TNF doses were used on the assumption that the disease burden was very low. While 1 and 2 mg/Kg doses were ineffective, a dose of 3 mg/Kg every 8-week restored and maintained mucosal integrity for 1 year (fig.1).

Surrogate markers of disease activity (fecal calprotectin, CRP and ESR) revealed that only fecal calprotectin levels correlate with mucosal disease at different infliximab doses. Thus, long-term maintenance therapy with infliximab is required to maintain mucosal integrity after surgery in patients with CD recurrence. However, a dose of 3 mg/Kg (a 40% reduction from the standard dose) appears sufficient to avoid endoscopic disease recurrence in all patients at one year.

Thus, this study provides a potential strategy to reduce costs and - likely - side effects in the long term. In addition, it also shows that infliximab therapy cannot be stopped without consequences. Indeed, stopping infliximab caused rapid endoscopic recurrence - which is an obligate precursor of clinical recurrence. Although it has been shown in the naturally occurring disease that infliximab could be stopped without immediate symptoms after mucosal healing (20) endoscopy was not performed in those patients in the follow-up (21,22).

Far Reaching Potential Implications of Available Data

The remarkable protection offered by anti-TNFs in preventing Crohn’s disease recurrence after surgery must be confirmed by larger trials. Potentially, this finding bears at least two crucial implications.

First, TNF-α plays a crucial role in the pathogenesis of CD, mechanistically more important than that of a simple proinflammatory cytokine (23). Current data suggest that TNF-α may act as a terminal effector of inflammation in CD - involved in the apoptosis of epithelial and immune cells, in the permeability of the mucosal barrier and in ulcer and granuloma formation (reviewed in ref.24). Recent evidence suggests that TNF-α may also control the number/function of Foxp3-CD25 (Treg) cells which in turn regulate effector T-cell response (25-27). It has also been proposed that an excessive production of TNF-α could confer resistance to the anti-inflammatory action of Treg-produced TGF-β or IL-10 via intracellular mediators of the action of these cytokines (28). Thus, TNF-α may act as a fulcrum of the fine balance between mucosal repair and destruction depending on the prevalence of Treg’s and Th17 function/number (29). Excessive TNF-α, as in CD and other chronic inflammatory states, would favour destruction whereas blockade of TNF-α (by anti-TNF’s antibodies) and other cytokines may re-establish such balance (29). Thus, TNF-α’s potentially crucial role in CD biology is consistent with the remarkable efficacy of infliximab in preventing disease before the onset of...
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Fig. 1. The mucosa of the ileocolic anastomosis at different infliximab doses. A: The patient was treated continuously immediately after surgery with 5 mg/Kg bw q8wk for 3 years. B: after stopping infliximab for 4 months therapy was restarted at 1 mg/Kg bw q8wk and continued for 6 months. C: therapy was increased to 2 mg/Kg bw q8wk and continued for 6 months. D: therapy was increased to 3 mg/Kg bw q8wk and continued for 6 months. E: same dose of 3 mg/Kg bw q8wk for one year. The progressive increase in infliximab dose re-established and maintained mucosal integrity for one full year. From Sorrentino et al (ref.17) with permission of the publisher.

macroscopic inflammation (30) after surgery (8,14).

Second, the remarkable efficacy of anti-TNF in preventing CD recurrence after surgery may change the paradigm of “early surgery” - which may become the new standard for both the patient and the treating physician. While the main indication for surgery for CD today is either a complication of long standing, aggressive disease (e.g. obstruction, perforation, fistulizing disease) or medical unresponsiveness (31) surgery performed on an elective basis offers a number of advantages. Morbidity and mortality may be reduced, the patient quality of life improves and surgery can be often performed laparoscopically with shorter hospital stay and recovery time (32). Indeed, when asked, many patients would have preferred to have their surgery performed earlier (32). By contrast, the knowledge that surgery leads to almost inescapable recurrence in most patients with the possibility of further resections and a resulting short bowel has traditionally discouraged such a strategy (33). Indeed, it was traditionally recommended that early resection should only be considered if it could be demonstrated that this intervention alters the natural history of the disease (33). Preventing recurrence after surgery in the large majority of patients would indeed qualify as a dramatic interruption of the natural history of the disease. Hence, patients with irreversible, fibrotic disease and at high risk of recurrence could undergo elective surgery regardless of impending clinical symptoms and be then treated with anti-TNF immediately after surgery. Although such an aggressive approach must clearly be weighted against long term costs and potential side effects of the medication the low dose infliximab strategy (17), if confirmed by future studies, could represent an excellent compromise.

Open Questions

Confirmation of the role of anti-TNFs in large RCTs remains the most compelling issue today (19,34). Another important question is whether anti-TNFs would be equally effective in treating, rather then preventing, recurrence - a strategy potentially safer and more cost effective.

Biancone et al. assessed the feasibility and the safety of local injection of infliximab for early mucosal postoperative recurrence in 8 patients and concluded that the procedure is both feasible and safe but endoscopy improved in only 3 out of 8 patients (35). Whether the lack of efficacy was due to the therapeutic delay or to low tissue levels of the drug is unknown.

Yamamoto et al (36) treated patients with mesalamine immediately after surgery and those (twenty-six) who developed endoscopic recurrence at 6 months were nonrandomly assigned to treatment with mesalamine, azathioprine or infliximab. After 6 months, infliximab-treated patients were recurrence free, while 38% of azathioprine-treated patients and 70% of mesalamine-treated patients had clinical recurrence. Endoscopic inflammation improved in 75% of the infliximab treated patients, in 38% of the azathioprine treated patients, and in none of mesalamine-treated patients. The authors concluded that infliximab may be effective in treating endoscopic recurrence. The design of this study and its short follow-up limit the conclusions (37). Nevertheless, when compared to the other studies, it suggests that infliximab may be less effective when given as a treatment of established lesions rather then when given for prevention.

Regueiro and colleagues followed for one year the patients initially treated with placebo (14) and offered them open-label infliximab. Their preliminary data

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(38) show - in keeping with ours (17) - that three of the infliximab treated patients who stopped infliximab developed endoscopic recurrence at 2 years. All patients from the placebo group who had endoscopic recurrence at 12 months and were then treated with infliximab had a reduction in their endoscopic scores but 50% of these patients still had scores of at least grade 2. The very small number of patients of this study does not allow firm conclusions.

Finally, a recent multicenter, nonrandomized open label pilot study in patients treated with infliximab or mesalamine for endoscopic recurrence occurring 6 months after surgery demonstrated at 12 months of therapy that infliximab is more effective then mesalamine in re-inducing endoscopic remission. However, although 69% of infliximab treated patients had an improvement in the endoscopic score and none had clinical recurrence, in a sizeable proportion of patients infliximab was not capable of restoring mucosal healing after one year of therapy. Hence, delayed infliximab treatment appears less effective then when used immediately after surgery (39).

CONCLUSIONS
Small studies indicate that anti-TNFs – given immediately after surgery – may prevent CD recurrence in the large majority of patients. Stopping the medication causes a rapid mucosal recurrence. Long term strategies, needing confirmation, may involve the use of low doses of anti-TNFs. It appears that infliximab given after recurrence has taken place is less effective then when given for prophylaxis immediately postoperatively.

References
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34. A multicenter trial comparing REMICADE (Infliximab) and placebo in the prevention of recurrence in Crohn’s disease (CD) patients undergoing surgical resection who are at an increased risk of recurrence clinicaltrials.gov/ct2/show/NCT01190839

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