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Prevention of postoperative recurrence with azathioprine or infliximab in patients with Crohn's disease: An open-label pilot study

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Abstract

Background and aims: Patients with Crohn's disease (CD) often require surgery over their clinical course. However, endoscopic and clinical recurrence of disease appear respectively in up to 80% and 30% of patients after one year. Thus, a prophylactic treatment is needed to reduce the possibility of recurrence. Both azathioprine and infliximab have been demonstrated to be effective, but head to head studies have not been performed so far. Aim of this open-label prospective study was to analyse endoscopic, histological and clinical recurrence after one year of treatment with azathioprine or infliximab as postoperative therapies in CD patients with "high risk" of recurrence.

Methods: Consecutive CD patients who underwent curative ileocolonic resection were randomized (1:1) to receive infliximab (standard induction and maintenance schedule) or azathioprine (2.5 mg/kg/day) for 1 year. Co-primary endpoints were endoscopic, histological and clinical recurrence after 12 months of therapy.

Results: Twenty-two consecutive CD patients (15 male; median age 32 years, IQR 22-38) were enrolled after curative ileocolonic resection. Eleven patients were treated with infliximab and 11 received azathioprine. Among patients treated with azathioprine, 4/10 (40%) had endoscopic recurrence compared to 1/11 (9%) in the infliximab group ($p = 0.14$). Eight out of 10 (80%) among those who received azathioprine had severe histological activity, whereas 2/11 (18%) in the infliximab group presented histological recurrence ($p = 0.008$). No significant clinical differences were found between the two groups.

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Conclusions: Infliximab was more effective than azathioprine in reducing histological, but not endoscopic and clinical recurrence after curative ileocolonic resection in "high risk" CD patients.

1. Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the bowel that may lead to severe tissue damage and often requires surgery for penetrating or stricturing complications. Available data demonstrated that the percentage of patients requiring surgery during the course of disease is still up to 75%.[1–3] Because of the main location of disease is terminal ileum with or without the proximal colon, the most common intervention for CD is an ileocolonic resection.[4] However, surgery may be not definitively curative and often CD patients develop recurrence of disease, typically in the preanastomotic ileum. In particular, recurrence may be "histological", "endoscopic", "clinical" or combined. It has been shown that endoscopic and clinical recurrence of CD appears respectively in up to 80% and 30% of patients 1 year after surgery.[5,6] Moreover, a considerable percentage of cases (34% at 10 years,[7] 33–82% at 15 years[8]) requires a re-operation over time, leading to a high probability of malabsorption syndrome and a poor quality of life. Endoscopic and histological lesions usually precede and predict the clinical manifestation of symptoms, and ileocolonoscopy with biopsies is therefore recommended as screening in CD patients within 12 months after surgery.[9]

Some risk factors for postoperative recurrence have been identified in several studies. In particular, active smoking,[10] penetrating behavior,[11–13] perianal location,[2,14] prior intestinal resection[15] and extensive small bowel resection (>50 cm)[2] have been demonstrated to increase the risk of recurrence after surgery for CD.

The utility of a medical therapy for prevention of postoperative recurrence is argument of debate. Mesalazine (5-ASA) demonstrated to be effective in reducing clinical relapse in operated CD patients[16,17]; several studies also evaluated endoscopic recurrence during treatment with 5-ASA, but results have been conflicting.[18,19] Nitroimidazolic antibiotics showed to be effective in the prevention of postoperative clinical and endoscopic recurrence. The benefit, however, seemed to decrease over time, in particular for metronidazole.[20,21] Most of published data about the use of azathioprine (AZA) or 6-mercaptopurine (6-MP) in the post-operative setting showed a greater efficacy compared to placebo or mesalazine,[22,23] in spite of a worse tolerability.[24] Recent studies documented that infliximab (IFX), an anti-tumor necrosis factor alpha, may be more effective than placebo in the reduction of endoscopic and also histological postoperative recurrence in CD patients.[25] No other studies about histological recurrence were published. New data are also emerging about the postoperative use of adalimumab to prevent or to treat early postoperative recurrence.[26–28]

To date, there are no clinical trials that directly compared infliximab and azathioprine as prophylactic treatment after CD-related surgery. The aim of our prospective open-label single-center study was to evaluate endoscopic, histological and clinical recurrence in CD patients who underwent curative ileocolonic resection and then received infliximab or azathioprine as preventive therapy for "high risk" postoperative recurrence.

2. Materials and methods

This was a prospective open-label pilot study conducted in a single center from November 2007 to June 2011. Consecutive CD patients who underwent curative ileocolonic resection and considered at "high risk" of postoperative recurrence were enrolled. Subjects were randomized with a simple unblinded 1:1 allocation ratio to receive infliximab (5 mg/kg at 0, 2 and 6 week and then every 8 weeks) or azathioprine (2.5 mg/kg/day) for 1 year. Treatment was started within 2–4 weeks after surgery. All patients also received oral metronidazole (500 mg bid) for 2 weeks after surgery. No other CD-related drugs were admitted during the study. Intestinal resection was considered "curative" if all macroscopically inflamed tissues were removed and operative margins were disease-free at histopathology examination. Ileocolonic stapled side-to-side anastomoses were performed. Patients were considered at "high risk" for postoperative recurrence if they had 2 or more than the following factors: young age at diagnosis (≤30 years), penetrating disease behavior, active smoking, perianal disease at diagnosis of CD, previous surgery and less than 3 years from previous surgery (Table 1).

Exclusion criteria included: active perianal disease, presence of stoma, adverse events during previous therapy with

Table 1 Risk factors for postoperative recurrence between study groups.

	IFX group (n = 11) n (%)	AZA group (n = 11) n (%)	*p*-Value [a]
Penetrating behavior	7 (63)	5 (45)	0.66
Young age at diagnosis (<30 years)	5 (45)	6 (54)	1
Active smokers	5 (45)	5 (45)	1
Perianal disease at diagnosis	5 (45)	6 (54)	1
Previous surgery	4 (36)	4 (36)	1
<3 years from previous surgery	1 (9)	1 (9)	1

IFX, infliximab; AZA, azathioprine.

[a] *p*-Values were calculated by Fischer's exact test.

infliximab or azathioprine, age >70 years, surgical complications, active infectious diseases, history of cancer, renal, cardiac or hepatic failure, history of acute or chronic pancreatitis, severe leucopenia (WBC <3000 μu/ml, lymphocyte count <1000 μu/ml) and pregnancy.

Co-primary endpoints were endoscopic, histological and clinical recurrence after 12 months of therapy between the two groups. Patients were monthly evaluated, according to laboratory tests, the Harvey–Bradshaw Index (HBI)[29] calculation and the adverse event report. Ileocolonoscopy was performed after 12 months of therapy and video recorded. One unblinded endoscopist (AP) did all the examinations and calculated scores. Two further unblinded endoscopists (IDV and GA) separately reviewed videos and in case of discordance a consensus agreement was reached among the three operators. Biopsies on preanastomotic ileum, anastomosis and colonic mucosa were performed. Endoscopic and clinical recurrence were defined by a Rutgeerts' score ≥i2[6] and a HBI ≥8, respectively. A histology score system modified from Regueiro et al.[25] was used to assess grading of active inflammation (Table 2). Endoscopic activity, histological score, C-reactive protein serum levels (CRP, normal value ≤5 mg/L) and clinical activity (HBI) were compared between the two groups after 12 months of treatment. All patients gave written informed consent to participate in the study.

2.1. Statistical methods

Frequencies were compared by Fisher's exact test. Differences among groups were tested by Mann–Whitney test. Significant *p*-value was set at 0.05 (MedCalc version 9.2.1.0, Mariakerke, Belgium).

3. Results

Twenty-two consecutive CD patients (15 male; median age 32 years, range 18–70) were enrolled after curative ileocolonic resection. Eleven patients were treated with infliximab and 11 received azathioprine. There were no differences between baseline characteristics of the two groups (Table 3): age, duration of disease, active smokers, previous surgery, disease behavior and location, perianal disease at diagnosis, extra-intestinal manifestations and previous treatments with infliximab or azathioprine. In particular, 10 patients received infliximab before surgery: among them, four were post-operatively treated with azathioprine and 6 started again anti-TNFα treatment, without any infusion reaction. The median time to surgery after the last infusion of infliximab was 10.5 weeks (IQR 8.47–12). Also risk factors that were considered for postoperative recurrence did not differ between the two groups. The indication to surgery was complicated CD, such as small-bowel obstruction or abscess formation due to penetrating behavior.

Neither re-operations nor postoperative surgery-related complications occurred during the study. One patient did not tolerate azathioprine because of severe nausea with epigastric pain and withdrew from the study after 5 weeks of treatment. No other significant adverse events were reported.

After 12 months of therapy, 21 patients underwent ileocolonoscopy with biopsies. Among those treated with azathioprine, 4/10 (40%) had endoscopic recurrence (Rutgeerts' score ≥i2) compared to 1/11 (9%) in the infliximab group (*p* = ns, Fig. 1). Three out of 4 patients receiving azathioprine had a Rutgeerts' score of i2, the other one had i4 (Table 4). The only patient who had endoscopic recurrence after treatment with infliximab presented a Rutgeerts' score of i2. A further comparison between patients with no sign of endoscopic inflammation (Rutgeerts' i0 group) and those ones with any sign of inflammation (Rutgeerts' i1–i4 group) in the two treatment arms (Table 4) did not show statistical significance (*p* = 0.08).

Considering the scoring system modified from Regueiro et al.[25], at the end of the study 8 of 10 (80%) patients treated with azathioprine had moderate to severe histological activity (score greater than 6, with at least grade 1 for polymorphonuclear scores), compared to 2 of 11 (18%) in the infliximab group (*p* = 0.008, Fig. 1).

No significant difference was found in clinical relapse rates between the two groups: 1 of 11 (9%) patients treated

Table 2 Histological grading of ileal biopsy specimens (modified from Regueiro et al.).[25]

Histological variable	Grading [a]
Crypt architectural changes	0 = normal; 1 = moderate (<50%); 2 = severe (>50%)
Mononuclear cells in lamina propria	0 = normal; 1 = moderate increase; 2 = severe increase
Polymorphonuclear cells in lamina propria	0 = normal; 1 = moderate increase; 2 = severe increase
Polymorphonuclear cells in epithelium	1 = surface epithelium; 2 = deep cryptitis; 3 = crypt abscess
Presence of erosions or ulcerations	0 = no; 1 = yes
Presence of granulomas	0 = no; 1 = yes
Pyloric gland metaplasia	0 = no; 1 = yes

[a] Moderate to severe disease activity was considered as score >6, with at least grade 1 for polymorphonuclear infiltration.

Table 3 Baseline characteristics of study groups.

Baseline demographic	IFX group (n = 11)	AZA group (n = 11)	*p*-Value [a]
Sex (male), n (%)	7 (63)	8 (72)	1
Previous treatment with infliximab, n (%)	6 (54)	4 (36)	0.67
Previous treatment with AZA, n (%)	3 (27)	2 (18)	1
Extraintestinal manifestations, n (%)	2 (18)	2 (18)	1
Age (year), median (IQR)	34, 24–37	32, 21–45	0.84
Duration of disease (month), median (IQR)	24, 15–81	24, 12–54	0.4
IFX infusion number before surgery, median (IQR)	(n = 6) 6.5, 6–8	(n = 4) 8.5, 7–9	0.47

IFX, infliximab; AZA, azathioprine.

[a] *p*-Values were calculated by Fischer's exact test for categorical variables and Mann–Whitney test for continuous variables.

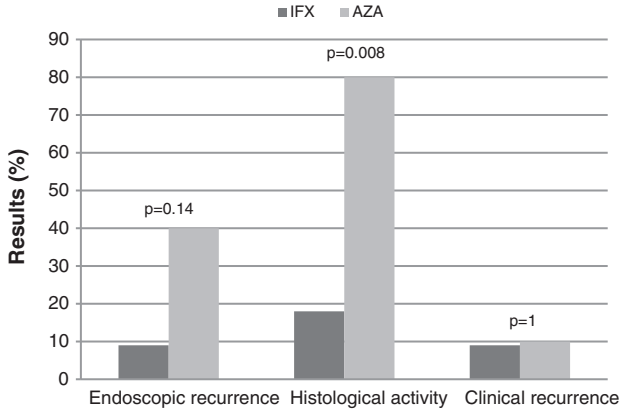

Figure 1 Comparison of results between groups after one year of therapy.

with infliximab and 1 of 10 (10%) of those who received azathioprine (Fig. 1). In particular, the subject treated with infliximab had a HBI of 9 without any evidence of endoscopic or histological recurrence, whereas the patient who had clinical relapse during azathioprine treatment presented both endoscopic and histological recurrence. On the other hand, the only subject who had endoscopic lesion and high histological score after one year of treatment with infliximab was clinically asymptomatic.

At the end of the study, median CRP resulted not different between groups: 1.07 mg/L (IQR 0.7–3.2) in patients treated with infliximab compared to 0.8 mg/L (IQR 0.6–3.4) in the azathioprine group (p = 0.86).

4. Discussion

Our study represents the first direct prospective comparison between infliximab, an anti-TNFα monoclonal antibody, and azathioprine, in the prevention of endoscopic, histological and clinical recurrence after ileocolonic resection in Crohn's patients. After one year of treatment 40% of subjects treated with azathioprine had endoscopic recurrence, compared to 9% of those who received infliximab. A statistically significant difference was shown in the histological recurrence rate between the two groups: in particular, 80% of patients treated with azathioprine presented high histological activity score compared to 18% in the infliximab group. No difference was found in the appearance of clinical relapse and CRP levels.

Table 4 Endoscopic activity in patients with recurrence of disease (Rutgeerts' score).[6]

Rutgeerts' score	Infliximab group (n = 11)	Azathioprine group (n = 10)
0	9	4
1	1	2
2	1	3
3	0	0
4	0	1

Surgery is often required in patients with Crohn's disease, but it may be not definitively curative. Considering the high probability of postoperative recurrence, a preventive therapy may be indicated especially when patients present some specific characteristics. In particular, among risk factors considered in our study, active smoking, penetrating behavior and previous surgery were demonstrated to significantly increase the possibility of postoperative recurrence.[30] Perianal disease and young age at diagnosis were also included although data about their impact on postoperative disease course come only from population-based cohorts or referral center studies.[30] There are no data about the role of a short time between surgeries, but in our opinion it represents an important index of aggressive disease course.

Data available so far showed a slight efficacy of mesalazine and an only short-term benefit from antibiotics in the prevention of post-operative recurrence in Crohn's disease.[31]

Meta-analyses about the use of thiopurines in the post-operative setting have shown their efficacy, but with a high rate of adverse events leading to drug withdrawal.[16,32] Azathioprine showed particularly better outcomes in patients selected for "high risk" to develop recurrence after surgery. In particular, Ardizzone et al. compared mesalazine versus azathioprine in the prevention of clinical or surgical recurrence in Crohn's patients who underwent conservative surgery. After 24 months of treatment, no differences were documented between the two groups; however, azathioprine was more effective than mesalazine in the prevention of clinical relapses in the subgroup of patients who have undergone previous surgery for CD (OR 4.83; 95% CI, 1.47–15.8).[33] D'Haens et al. evaluated percentages of endoscopic recurrence at 3 and 12 months in CD patients who underwent ileocecal resection and then were treated with metronidazole for 3 months followed by azathioprine or placebo until the end of the study. Only subjects considered at "high risk" for recurrence, defined as the presence of $\geq$1 of several factors, were included in this trial. Results showed better endoscopic outcomes in the group of patients who received azathioprine: in particular, at 12 months endoscopic recurrence appeared in 69% and 43.7% of patients treated with placebo or azathioprine, respectively.[23] All subjects included in our study received 2-week treatment with metronidazole: the common approach of antibiotic treatment for post-operative prevention of recurrence in our IBD Unit is usually longer than 2 weeks, but the short duration of metronidazole administration was chosen to reduce any possible influence on outcomes and to avoid drop-out because of nitroimidazole-related side effects.

Hanauer et al. compared 6-mercaptopurine (6-MP) with mesalamine and placebo in the postoperative maintenance of remission in CD patients for 24 months after surgery. Results showed a statistically significant efficacy of the immunosuppressant in comparison with placebo: in particular, 43% of patients receiving 6-MP had endoscopic recurrence at the end of the study versus 64% of those treated with placebo ($p < 0.05$).[22] Our data showed a percentage of patients who had endoscopic recurrence after one year of therapy with azathioprine (40%) similar to that reported in previous studies.[22,23]

Data about the use of anti-TNFα in the prevention of postoperative recurrence in CD patients are still limited. The first case series showed better outcomes in CD patients who

were post-operatively treated with infliximab and low doses of methotrexate in comparison with those who received only mesalamine (0 of 7 versus 7 of 16 patients had endoscopic recurrence after 2 years, respectively).[34]

A randomized, double-blind, placebo-controlled trial included 24 CD patients who underwent curative ileocolonic resection and then were randomized to receive infliximab or placebo for one year as preventive therapy for postoperative endoscopic recurrence. As secondary outcomes, clinical relapse, histological activity score and laboratory tests were evaluated. Results showed a statistically significant difference in terms of endoscopic recurrence between the two groups: 1 of 11 (9.1%) patients in the infliximab group compared to 11 of 13 (84.6%) ones in the placebo group presented endoscopic recurrence ($p = 0.0006$).[25] Thus, the percentage of patients treated with infliximab that had endoscopic recurrence in this trial was the same reported in our study. As far as histological activity is concerned, 27.3% of patients in the infliximab group presented high scores of inflammation in comparison with 18% in our study.

However, there are some important differences between these studies. At first, we considered eligible to receive immunosuppressive or anti-TNFα therapy after surgery only CD patients with $\geq$2 risk factors for post-operative recurrence (Table 1). Moreover, in our study 40% of subjects receiving azathioprine presented endoscopic recurrence after one year, in comparison with 84.6% of those treated with placebo in the other trial. This could be a significant difference considering that actually 11 of 13 patients in the placebo group were taking unspecified immunosuppressant therapy or mesalamine. Finally, in our study there was no difference in both clinical relapse and CRP levels after 12 months of treatment between the two groups, whereas Regueiro et al. found significant better clinical and laboratory outcomes in CD patients who received infliximab. These results may be partially explained considering that scores to evaluate clinical symptoms were different: we used the Harvey–Bradshaw Index,[29] in comparison with the CDAI (Crohn's Disease Activity Index) score[35] used in the other study. It should be specified that both these clinical scores were not validated in studies on post-operative recurrence, therefore their reliability is not warranted. In our trial, the only subject treated with infliximab who had clinical relapse didn't present any evidence of endoscopic recurrence: it could mean that unspecific symptoms, such as abdominal pain or diarrhea may occur in CD patients after intestinal resection, due to short bowel syndrome, post-operative adhesions or bacterial overgrowth.

An interesting characteristic of patients included in our evaluation was that 6 and 4 patients in the infliximab and azathioprine group, respectively, have been already treated with anti-TNFα before surgery (Table 3). All patients underwent intestinal resection for CD-related complications. During the study, all patients who continued to receive infliximab didn't present any reaction to infusion, similar as data reported in previous studies.[25] Considering these results, we can speculate that surgery may not always represent a failure of the anti-TNFα treatment and it could mean just a too delayed onset of biological therapy over disease course.[36] Moreover, the scheduled administration of infliximab shortly after surgery, when there are no signs of active disease, could really interfere with initial pathogenetic mechanisms of tissue damage, changing the natural evolution of disease. At this regard, although data are still limited, it was described that baseline levels of serum and mucosal cytokines, such as IL-1β, IL-6 and TNFα, may play a role in the pathogenesis of post-operative Crohn's disease, predicting the risk of recurrence.[37]

Data are emerging also about the use of adalimumab in the postoperative setting. An observational study was conducted in 29 CD patients with high risk of recurrence after ileocolonic resection: adalimumab was administrated shortly after surgery (within 2 weeks) as preventive treatment, and after one year 20.7% and 13.7% of patients had endoscopic and clinical recurrence, respectively.[26] Papamichael et al.[27] recently described a prospective, open-label, two-year study including 23 operated CD patients who received adalimumab as preventive therapy because of high risk of postoperative recurrence or as treatment for evidence of endoscopic lesions at 6 months after surgery, with or without clinical relapse. Adalimumab was demonstrated to be effective in both prevention and treatment of postoperative recurrence of CD in "high risk" patients. The POCER (Post Operative Crohn's Endoscopic Recurrence) study[28] included CD patients who underwent curative resection and then received thiopurines if were considered at high risk of recurrence; adalimumab was subsequently administered to those who didn't tolerate azathioprine or 6-mercaptopurine. Early results showed that 17/45 (38%) high risk patients treated with thiopurines presented endoscopic recurrence at 6 months compared to 1/16 (6.2%) among those treated with adalimumab ($p = 0.024$), confirming the superiority of anti-TNFα in preventing postoperative recurrence in high risk CD patients.

In our evaluation, few patients have been already treated with thiopurines before surgery, thus conclusions about retreatment with azathioprine after surgery are not feasible; however, it should be mentioned that both patients who were postoperatively retreated with azathioprine presented endoscopic recurrence at one year.

Our study presents several limitations. The most important is the open-label format: the absence of a double-dummy administration of study drugs and the unblinded clinical and endoscopic evaluations of patients may have impacted results. However, based on these proofs of concept data a future double-blind placebo-controlled trial could be promoted.

Furthermore, considering that it was conducted in a single referral center and that subjects were selected for risk factors for postoperative recurrence, the number of patients is low, leading to a poor statistical significance of results. More extensive data are needed. At this regards, a multicenter trial comparing infliximab and placebo in the prevention of post-operative recurrence in high risk CD patients is currently taking place,[38] but our study remains the first direct comparison between infliximab and azathioprine in the management of CD after surgery.

Considering that the risk of postoperative recurrence increases over time,[6] long-term data are needed to really evaluate the effect of preventive treatments on the natural course of CD. Yoshida et al.[39] recently published a prospective open trial about the use of 3-year scheduled infliximab monotherapy as preventive therapy in Crohn's patients after an ileal or ileocolonic resection, considering clinical remission as primary outcome and endoscopic activity as secondary outcome. Thirty-one subjects were randomized to receive

anti-TNFα or to continue their ongoing conventional medication which started at least 8 weeks before surgery. After 12 months of treatment, no difference was found in remission rate between the two groups, whereas 81.3% of those conventionally treated presented endoscopic recurrence in comparison with 21.4% in the infliximab group. Unfortunately, the second endoscopic evaluation was not performed after a standardized interval of time and in all patients: however, endoscopic remission was demonstrated in 2 of 4 patients treated with infliximab (50%) after a median of 29.3 months, in comparison with 0/6 in the control group (0%) after a median of 20.7 months.[39]

In conclusion, our study represents the first direct comparison between two important therapeutic approaches in the prevention of postoperative recurrence in Crohn's disease. Although few subjects were included in this evaluation and more data are needed, our results suggest that in CD patients with high risk for recurrence after ileo-colonic surgery infliximab may be more effective than azathioprine in the prevention of histological lesions after one year of treatment.

Conflict of interest statement

AA received: consultancy from Abbvie, MSD; lecture fees from Abbvie, MSD, Chiesi, Ferring, Nycomed, Otsuka; educational grants from Abbvie, MSD, Ferring, Nycomed.

LG received: educational grants from Abbvie, MSD.

CF, AP, MM, DP, GA, FF, IDV, GLR: nothing to declare.

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AA and CF designed the study, acquired, analyzed, and interpreted the data and wrote the manuscript. AP, MM, DP, LG, IDV, GA and GLR contributed to obtain clinical and endoscopic data. FF made the histological examination. LG performed statistical analysis. All authors contributed to draft and revise the article. All Authors approved the final submitted version.

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