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Adalimumab for the prevention and/or treatment of post-operative recurrence of Crohn's disease: A prospective, two-year, single center, pilot study☆

Konstantinos Papamichael [a], Emmanuel Archavlis [a], Constantina Lariou [b], Gerassimos J. Mantzaris [a,*]

[a] A′ Department of Gastroenterology, Evangelismos Hospital, Athens, Greece
[b] Department of Histopathology, Evangelismos Hospital, Athens, Greece

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Abstract

Background: Infliximab has shown efficacy at preventing post operative recurrence (POR) of Crohn's disease (CD). This study aimed at evaluating whether adalimumab can prevent and treat POR of CD.
Methods: This prospective, single-center, open-label, two-year study included 23 patients who had undergone ileocecal resection for refractory or complicated CD and were at high-risk for POR. Patients received adalimumab from post operative day 14 (Group I, n=8) or at 6 months post operatively after confirmation of endoscopic recurrence (PO-ER) despite treatment with azathioprine, infliximab, or 5-ASA (patients intolerant to infliximab and azathioprine, Group II, n=15). Symptom assessment and laboratory tests were performed at monthly visits. Endoscopic findings were graded using the Rutgeerts score (RS) at 6 and 24 months after initiation of adalimumab. Primary end-points were maintenance (group I) or achievement of mucosal healing (Group II). Secondary end-points were prevention of post operative clinical recurrence (PO-CR) (Group I) and endoscopic and clinical improvement (group II).
Results: In Group I, PO-ER (RS≥i2) was seen in one patient at 6 months PO, whereas a second patient developed PO-ER and PO-CR after 24 months of treatment. In Group II, all patients had PO-ER whereas 9 (60%) patients had PO-CR at study enrolment; after 24 months of treatment 9/15 (60%) patients achieved complete (RS-i0, n=3) or near complete (RS-i1, n=6) mucosal healing and 5/9 (56%) clinical remission. No serious adverse events were reported.

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* Corresponding author at: 8b Strymonos Street, Kifissia-145 61, Athens, Greece. Tel.: +30 213 2045223; fax: +30 213 2041604; mobile: +6937 251720.
E-mail address: gjmantzaris@gmail.com (G.J. Mantzaris).

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Conclusions: This pilot study suggests that adalimumab may prevent PO-ER and treat PO-ER/CR in high risk patients for POR of CD.

1. Introduction

Approximately three quarters of patients with stricturing or penetrating phenotype of Crohn's disease (CD) affecting the terminal ileum and/or the right colon will require at some time intestinal resection.[1] However, even after 'curative' surgical resection, that is removal of all macroscopic lesions, CD will inevitably relapse at some time during the post operative period. Post operative recurrence (POR) may be more rapid and more severe for patients carrying additional risk factors, such as young age, active smoking, ileal disease, perforating disease phenotype, repeated ileal resections and active perianal disease.[2,3]

POR of CD may be detected in all patients by histology during the first post-operative week.[4] More than 70% of patients will develop endoscopically detected recurrence of disease at the site of the anastomosis and/or in the neo-terminal ileum by the end of the first post operative year whereas up to 35% of patients will have relapsed clinically after three years.[5] Thus, post operative endoscopic recurrence (PO-ER) precedes clinical relapse and mandates the development of new complications of disease that may lead onto further intestinal resections in 15% to 65% of patients after 10 years.[6,7] Because PO-ER is a marker of impending clinical deterioration ileocolonoscopy has become the gold standard for assessing POR of CD[5,8] and has been recommended at 6–12 months after surgery.[9]

To prevent POR of CD it has been recommended that all patients receive treatment starting from the end of the second post operative week.[10] However, the ideal 'preventive' therapy has not been yet clearly defined. 5-aminosalicylates (5-ASA) and budesonide have shown little or no benefit.[11–13] Administration of metronidazole and ornidazole in the immediate post operative period may reduce or delay POR.[14,15] Azathioprine (AZA) has shown superiority over placebo and mesalazine at preventing or delaying PO-ER of CD[16–18] but other studies have cast doubts whether this is translated into prevention of clinical recurrence of disease.[19,20] Regarding biologicals, classical infliximab (IFX) induction followed by scheduled maintenance therapy after intestinal resective surgery was shown to be by far superior to placebo at preventing endoscopic and histological recurrence of CD at the end of the first post operative year.[21] In addition, IFX was more effective than AZA or mesalamine at improving both clinical and endoscopic activities of CD and decreasing the levels of the cytokines IL-1, IL-6, and TNF-α in the intestinal mucosa of patients who had developed endoscopic lesions at an early stage after surgery.[22] Additional open-lapel data have confirmed the efficacy of IFX in the prevention of PO-CR and PO-ER of CD.[23] Finally, Fernandez-Blanco et al. have recently reported (in an abstract form), that only 2 out of 20 (10%) patients who were treated with adalimumab (ADA) after resective surgery for complications of CD had an PO-ER, and none had PO-CR after 1 year of treatment.[24] However, to our knowledge there is no study regarding the efficacy of ADA in the treatment of PO-ER and PO-CR of CD.

2. Patients and methods

2.1. Study design

This was a prospective, open-label, two-year pilot-study that was conducted at a single-center according to the Second Declaration of Helsinki. This study aimed at assessing the role of ADA, a fully human anti-TNFα monoclonal antibody, for the prevention and treatment of POR of CD. The study was approved by the Institution Review Board. All patients gave written informed consent.

2.2. Patients

Eligible for this study were patients who had undergone a recent 'curative' ileocecal resection for treatment refractory or complicated (fistulating/obstructive) Crohn's ileitis or ileocolitis and were at high risk for early POR as well as patients who had a prior ileocecal resection but had early PO-ER confirmed by scheduled ileocolonoscopy at 6 months post operatively despite timely initiated, adequately dosed and continuously administered treatment with AZA, IFX, or 5-ASA, for thiopurine and IFX intolerant patients. CD was confirmed by pre-operative ileocolonoscopy and histology on endoscopic mucosal biopsies, small bowel enteroclysis or magnetic resonance enterography and histological assessment of the resected intestinal specimen. 'Curative' resection was defined as removal of all grossly macroscopic residual disease leaving histological disease-free anastomotic endings. The pre-operative length of involvement had been assessed by ileocolonoscopy and small bowel enteroclysis or magnetic resonance enterography. Risk factors for early POR included young age (below 30 years), active smoking, penetrating disease phenotype and previous surgery for CD. Exclusion criteria were ileal/colonic resection with a temporal ileostomy, ileorectal anastomosis, absence of risk factors for early POR, severe active perianal disease, colorectal stenosis precluding ileocolonoscopy, advanced chronic renal, pulmonary or heart failure, infectious complications, colorectal cancer or any other known malignancies, pregnancy or lactation and prior use of ADA.

2.3. Methods

Enrolled patients were allocated into two study groups. Group I consisted of patients who had undergone a recent ileocecal resection for CD with ileocolic anastomosis as defined earlier. Patients received ADA induction [160 mg and 80 mg subcutaneously (sc) at weeks 0 and 2] followed by scheduled therapy (40 mg sc every other week) from postoperative day 14. Group II consisted of patients with a recent ileocecal resection that despite appropriate treatment, as defined previously, had had a PO-ER confirmed by scheduled ileocolonoscopy at 6 months post operatively. Patients received ADA as previously

but a washout period of 4 weeks between stopping IFX or AZA was allowed before initiation of ADA. No concomitant treatment was allowed. Treatment escalation to 40 mg ADA weekly was allowed during follow up for Group I patients who had an endoscopically confirmed PO-ER of disease as well as for Group II patients who had persistent clinical and endoscopic activities of disease. A flowchart of patients and reasons for treatment escalation enrolled in the study is given in Figure 1.

Patients were seen in the Outpatient IBD Clinic at monthly intervals. At each visit the Harvey-Bradshaw Index (H-BI)[25] was calculated on data collected the day before the visit; physical examination was performed; adherence to treatment was assessed; a list of side effects to treatment was checked; and laboratory tests performed the day before the visit were reviewed. The latter included a full blood count, erythrocyte sedimentation rate (ESR) and serum C-Reactive Protein (CRP). Additional biochemical tests were requested at 6 months interval or at any time if indicated.

Ileocolonoscopies were performed at 6 and 24 months after initiation of ADA or at any time new symptoms and/or abnormal serological tests suggested either POR of CD (Group I), or persistent disease activity (Group II), or an adverse event to treatment (both groups), by a single endoscopist (GJM) unaware that the patient was enrolled in a clinical trial or of his/her current treatment, or prior colonoscopy reports. At endoscopy, the distal 25–30 cm of the neo-terminal ileum was examined and lesions, if found, at the site of ileocolic anastomosis and/or in the neo-terminal ileum were recorded and graded according to Rutgeerts.[6] Briefly, i0 score indicated complete mucosal healing; i1: less than 5 apthoid ulcers in the neo-terminal ileum (near complete mucosal healing); i2: more than 5 apthoid ulcers with normal mucosa between lesions or lesions confined to the ileo-colonic anastomosis; i3: diffuse ileitis with larger ulcers but with normal mucosa between lesions and i4: diffuse ileitis with large ulcers, nodules and narrowing of the lumen without normal mucosa. PO-ER in Group I was defined as a Rutgeerts' score equal or higher than i2 (RS $\geq$ i2). In group II, endoscopic improvement was defined as any reduction in the Rutgeerts' score compared to baseline score whereas complete mucosal healing was regarded as a RS-i0. Biopsies were also taken from the neo-ileum to confirm histological activity of disease even in the absence of endoscopic lesions.[21]

PO-CR of CD was defined as a H-BI higher than 8 and a score equal or higher than 2 on the clinical recurrence grading scale (CRGS) proposed by Hanauer et al.[16] In this scale, score 1 indicates absent; 2: mild; 3: moderate, and 4: severe symptoms.[16] Serological remission was defined as normal levels of ESR $<$ 20 mm/1 h and serum CRP $<$ 0.5 mg/dl. We did not choose the Crohn's Disease Activity Index (CDAI) score because of the complexity and unreliability of this index in the post operative period and because no consistent associations have been observed between endoscopy scores and mean CDAI, or serum CRP, or ESR levels.[26,27]

2.4. Statistical analysis

The primary end-point in Group I patients was the prevention of early (at 6 months) and late (at 24 months) PO-ER of CD whereas and in Group II the rate of complete mucosal healing. Secondary end-points were assessment for PO-CR in Group I, and endoscopic and clinical improvement in Group II. Comparisons between groups of patients were made using independent sample *t*-test, Mann–Whitney non-parametric test and the Fisher Exact test, as appropriate, with $P < 0.05$ being regarded as a critical level of significance.

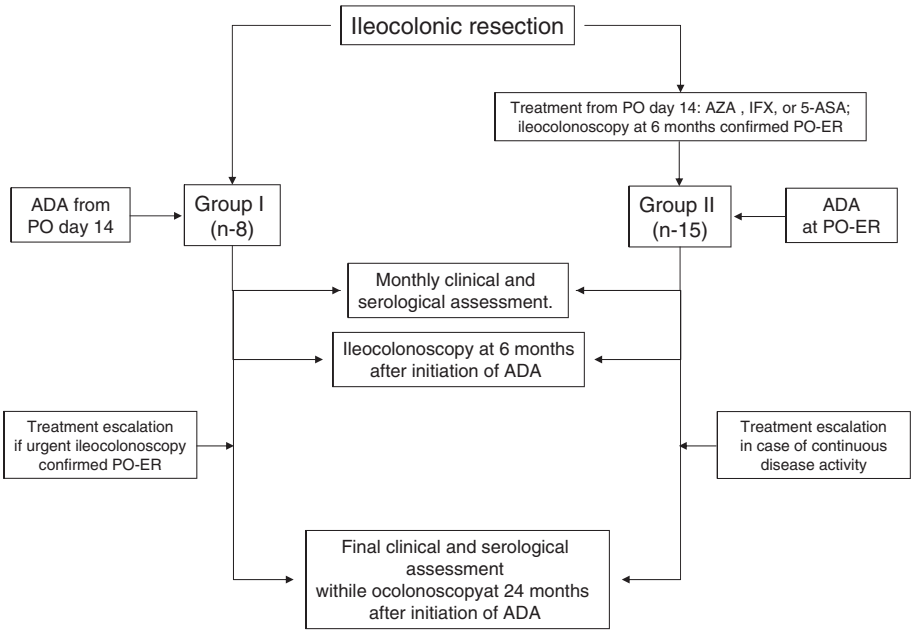

Figure 1 Flow-chart of patients treated with adalimumab to prevent (Group I) and heal (Group II) post-operative recurrence of Crohn's disease. ADA: adalimumab; 5-ASA: 5-aminosalicylic acid; AZA: azathioprine; IFX: infliximab; PO: post-operative; PO-ER: post-operative endoscopic recurrence.

3. Results

Twenty three patients were enrolled in this study between 1st June 2007 and 31st October 2009. Patient demographic and clinical characteristics are given in Table 1. Eight patients received ADA starting from the 14th post-operative day (Group I). Fifteen patients (Group II) received ADA when a post operative ileocolonoscopy, performed according to scheduled endoscopic follow up at six months post operatively confirmed PO-ER (RS $\geq$ i2) despite treatment with AZA (n = 10), IFX (n = 3), or 5-ASA (n = 2) for AZA and IFX intolerant patients (Table 1). More specifically, 11 patients had RS-i2 and 4 had RS-i3 lesions before treatment with ADA. In addition to endoscopic recurrence, 9 of 15 patients had also clinical relapse of CD (H-BI > 8 and CRGS $\geq$ 2) (Figure 2, Table 2).

At 6 months, 7 of 8 patients (87.5%) in Group I did not have any evidence of PO-ER or PO-CR of CD: five patients had a normal ileocolonoscopy (R-i0) and two had mild endoscopic activity of disease (RS-i1) (Figure 2, Table 2). Only one patient had PO-ER of CD (RS-i2) and was started on 40 mg ADA every week. However, all 8 patients in Group I maintained clinical and serological remission of CD, as indicated by a H-BI < 4, a CRGS < 2 and normal levels of ESR and CRP (Table 2). After 1 year of treatment with ADA, endoscopic, clinical and serological relapses were confirmed in another patient. Treatment escalation to 40 mg ADA every week did not restore clinical or serological remission in this patient and none of these two relapsers in Group I achieved complete or near complete mucosal healing after two years on ADA therapy (Figure 2, Table 2). Thus, at 2 years after ADA therapy in Group I, 6 of 8 (75%) patients maintained either complete (n = 3, RS-i0) or near complete (n = 3, RS-i1) mucosal healing and 7 of 8 patients (87.5%) remained in clinical and serological remission of CD (Figure 2, Table 2).

In Group II, 6 months after starting ADA, one patient had a RS-i0, two had a RS-i1, 10 had a RS-i2 and two patients had a RS-13 (Figure 2, Table 2). Thus, ADA healed the mucosa or improved the Rutgeerts score in three patients with RS-i2 and two patients with RS-i3. After 24 months of treatment, ADA had healed completely (RS-i0) endoscopic lesions in 3 (27%) patients and improved the score (RS-i1) in another 3 (27%) of 11 patients with an initial RS-i2 and in 3 of 4 patients with RS-i3 (one patient had RS-i1 and two had RS-i2) (Figure 2, Table 2). Overall, 9 (60%) patients had RS-i0 (n = 3) or RS-i1 (n = 6) but persisting lesions were found in 6 (40%) patients, with 5 patients having RS-i2 and one patient RS-i3 lesions, respectively (Figure 2, Table 2).

Before initiation of ADA treatment, 9 patients had clinically active disease and 5 of these 9 patients had also elevated levels of CRP and ESR (Table 2). Five of these 9 (56%) patients including two with serologically active disease achieved and maintained clinical and serological remission during treatment with ADA. After 6 months of ADA therapy, three patients had continued clinically, serologically and endoscopically active disease whereas one patient had clinical and endoscopic but no serological activity of disease. Despite treatment escalation none of these 4 patients improved clinically or endoscopically. In contrast, deterioration of disease and development of stricturing complications led eventually two of these patients to a new surgical resection (Figure 2). Regarding Group II, although no risk factors for POR under ADA treatment were revealed as none of patient and disease characteristics was related to PO-ER (Table 3) numbers are very small to allow firm conclusions. Interestingly, in Group II ADA did heal pre-anastomotic lesions but did not have any effect on anastomotic lesions.

Smoking did not affect the rate or the severity of POR. None of the smokers was able to quit smoking during the study. During the two-year follow up, there were no drop outs for drug complications, such as adverse events and/or allergic reactions from the study.

Table 1 Patient and disease characteristics in Groups I and II.

Patients characteristics	Group I	Group II
Male/female	4/4	9/6
Age: years, median (range)	38.5 (20–53)	32 (17–58)
Disease duration: years, median (range)	6 (1–15)	11 (1–20)
Disease location, n (%)		
Ileitis	5 (62.5)	5 (33.3)
Ileocolitis	3 (37.5)	10 (66.6)
Perianal	3 (37.5)	5 (33.3)
Smokers, n (%)	5 (62.5)	8 (53.3)
Extraintestinal manifestations, n (%)	5 (62.5)	5 (33.3)
Before surgery, n (%)		
Corticosteroids	8 (100)	15 (100)
Azathioprine	5 (62.5)	7 (46.7)
Infliximab	3 (37.5)	8 (53.3)
After surgery, n (%)		
5-ASA	0 (0)	2 (13.3)
Azathioprine	0 (0)	10 (66.7)
Infliximab	0 (0)	3 (20)
Adalimumab	8 (100)	0 (0)
Indications for surgery, n (%)		
Inflammatory obstruction and/or fistulating disease	4 (50)	10 (66.7)
Penetrating disease (fistula ± abscess)	4 (50)	5 (33.3)
Previous ileocolonic resection, n (%)	0 (0)	5 (33.3)

4. Discussion

Although there is no established therapy for the post operative treatment of patients with CD, various investigators have suggested that AZA and IFX can prevent and/or treat POR in CD.[16–18,21–23] Regarding efficacy of ADA, there is only one report looking at the prevention of POR of CD where 20 patients were treated with ADA after curative intestinal resection for complicated CD[24] and one case report of a patient with early severe POR of CD involving the colon and associated cytomegalovirus infection who was treated with oral valganciclovir and ADA.[28] In this prospective, single center, open-label, pilot study aiming at assessing the short and long term efficacy of ADA in the post operative setting for patients at high risk for early POR of disease, ADA proved efficacious both at preventing PO-ER in patients with CD who had undergone resective surgery, and in treating POR in CD patients who had developed

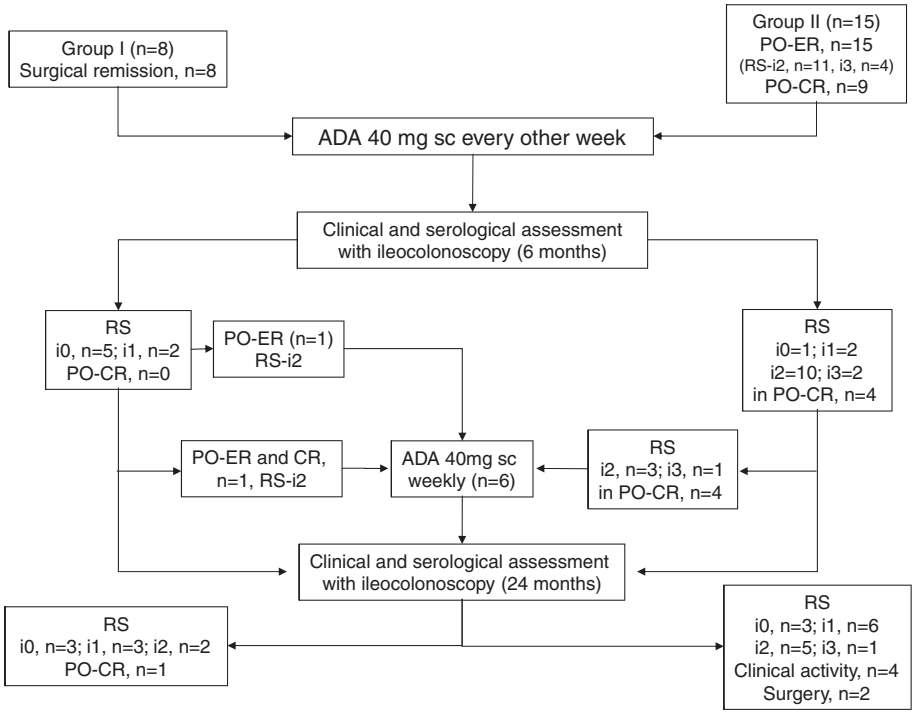

Figure 2 Flow-chart of outcome of treatment with adalimumab for the prevention (Group I) and treatment (Group II) of post-operative recurrence of Crohn's disease. ADA: adalimumab; sc: subcutaneously; RS: Rutgeerts score; i: ileal; PO-ER: post-operative endoscopic recurrence; PO-CR: post-operative clinical recurrence.

endoscopic and/or clinical POR despite appropriate therapy. The fact that ADA did not exert any healing effect on anastomotic lesions in Group II patients indicates that these lesions are not entirely 'immunologic' in nature but may be related to surgical techniques, local ischemia, or any other yet unidentified mechanisms.

Regarding the preventing role of IFX, Sorrentino et al. showed initially that the combination of IFX in classical scheduled maintenance dose (5 mg/kg every 8 weeks) and low-dose oral methotrexate (10 mg/wk) started at 2 weeks after surgery, was effective in preventing PO-ER and PO-CR of CD for 2 years.[23] In a follow up study, Sorrentino et al. treated CD patients in the immediate post operative period with IFX schedule maintenance therapy (5 mg/kg every 8 weeks) and noticed that none had PO-ER for 24 months.[29] However, 4 months after discontinuation of IFX 10 out of 12 patients (83%) developed PO-ER (RS≥i2). Re-treatment with lower doses of IFX (3 mg/kg, every 8 weeks) restored and maintained endoscopic remission of CD for 1 year.[29] In the only randomized placebo-controlled trial to date, Regueiro et al. showed that one-year treatment with the classical IFX regimen after surgery was far more effective than placebo at preventing endoscopic and histologic recurrence of CD (9.1% and 27.3% vs 84.6% and 84.6%, respectively) although the rate of PO-CR of CD was only numerically lower in the IFX arm in comparison to the placebo-treated patients (20.0% vs 46.2%).[21] It should also be noted that significantly more patients who were using concomitantly immunomodulators and were smokers had been enrolled in the IFX arm. Data from a two-year follow-up of this study have recently been presented, suggesting that the improved outcomes can be maintained in subjects who continue IFX therapy.[30] Furthermore, in a prospective study Biancone et al. showed that local injections of low dose IFX into the site(s) of

Table 2 Patient clinical and laboratory data before (Group II) and after (Groups I and II) adalimumab treatment.

	Group I		Group II		
	(6 months)	(24 months)	(Before ADA)	(6 months)	(24 months)
H-BI>8, n (%)	0 (0)	1 (12.5)	9 (60)	4 (26.6)	4 (26.6)
CRGS[16]>2, n (%)	0 (0)	1 (12.5)	9 (60)	4 (26.6)	4 (26.6)
CRP>0.5 mg/dl, n (%)	0 (0)	1 (12.5)	5 (33.3)	3 (20)	3 (20)
ESR>20 mm/1 h, n (%)	0 (0)	1 (12.5)	5 (33.3)	3 (20)	3 (20)
Histological recurrence,[21] n (%)	3 (37.5)	5 (62.5)	15 (100)	14 (93.3)	12 (80)
Second ileocolonic resection, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	2 (13.3)
Adverse events of ADA, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

H-BI: Harvey-Bradshaw index, CRGS: clinical recurrence grading scale, CRP: C-Reactive Protein, ESR: erythrocyte sedimentation rate, ADA: adalimumab.

Table 3 Patient and disease characteristics in Group II in response to adalimumab, related to endoscopic post-operative recurrence, after 24 months of treatment.

Patients and disease characteristics	Non responders	Responders	*P*
Male/female	3/3	6/3	NS
Age: median (range) (years)	34 (17–58)	32 (21–48)	NS
Disease duration: median (range) (years)	7.5 (1–19)	12 (5–20)	NS
Disease location, n (%)			
Ileitis	2 (33.3)	3 (33.3)	NS
Ileocolitis	4 (66.6)	6 (66.6)	NS
Perianal	1 (16.7)	4 (44.4)	NS
Smokers, n (%)	4 (66.6)	4 (44.4)	NS
Extraintestinal manifestations, n (%)	2 (33.3)	3 (33.3)	NS
Indications for surgery, n (%)			
Inflammatory obstruction and/or fistulating disease	5 (83.3)	5 (55.6)	NS
Penetrating disease (fistula ± abscess)	1 (16.7)	4 (44.4)	NS
CRP (mg/dl, mean ± SD)	1.94 ± 2.57	0.24 ± 0.09	NS
ESR (mm/1 h, mean ± SD)	30.63 ± 19.91	12.14 ± 3.80	0.034
H-BI (mean ± SD)	6.63 ± 3.77	2.57 ± 1.39	0.019
CRGS[16] (mean ± SD)	2.12 ± 0.35	0.57 ± 0.53	<0.001
Previous treatment before ADA, n (%)			
5-ASA	1 (16.7)	1 (11.1)	NS
Azathioprine	5 (83.3)	5 (55.6)	NS
Infliximab	0 (0)	3 (33.3)	NS
Rutgeerts score at 6 months PO, n (%)			
i2	3 (50)	8 (88.9)	NS
i3	3 (50)	1 (11.1)	NS
i4	0 (0)	0 (0)	NS
Rutgeerts score 6 months after ADA therapy, n (%)			
i0	0 (0)	1 (11.1)	NS
i1	0 (0)	2 (22.3)	NS
i2	4 (66.6)	6 (66.6)	NS
i3	2 (33.3)	0 (0)	NS
i4	0 (0)	0 (0)	NS

H-BI: Harvey-Bradshaw index, CRGS: clinical recurrence grading scale, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, ADA: adalimumab, SD: standard deviation, PO: post operative, NS: non significant.

endoscopic recurrence prevented the short and medium term clinical relapses of CD without compromising safety for a median follow up period of 20 months; in addition, local treatment improved both the Rutgeerts endoscopic and the histologic score in 3 and 4 out of 8 patients.[31]

Regarding the efficacy of anti-TNF agents to heal or improve POR of CD, Yamamoto et al. showed that IFX was more effective than AZA and 5-ASA in reducing the clinical and endoscopic disease activities in patients with early PO-ER: six months after treatment none of the eight IFX-treated patients compared with 3/8 (38%) of AZA-treated and 7/10 (70%) of 5-ASA-treated patients developed PO-CR (CDAI ≥ 150, $P=0.01$).[22] Moreover, endoscopic inflammation was improved in 6/8 (75%) of IFX-treated vs 3/8 (38%) of AZA-treated and none of the ten 5-ASA treated patients ($P=0.006$), whereas complete mucosal healing was achieved in 38% of patients in the IFX group, 13% in the AZA and in none of 5-ASA treated patients ($P=0.10$). Based on these results several issues remain unresolved, for instance if IFX is equally efficacy in treating early endoscopic and/or clinical POR as it is in preventing POR of CD and whether combination therapy with IFX and an immunomodulator is more effective than IFX monotherapy, as has been shown in active CD.[29,32]

In the only up to date ADA report, 20 patients were treated with ADA after curative intestinal resection for complications of CD. Patients received a standard induction regimen (160 mg, followed 2 weeks later by 80 mg) and then maintenance therapy of 40 mg every other week. After 1 year of treatment there were no clinical recurrences but two patients (10%) had a PO-ER (RS > i1) and 45% of the patients had at least moderate histologic recurrence.[24] The results in our study are more or less similar to those in the Spanish ADA study and prior IFX studies although our patients may have been more prone to POR because of a cluster of poor prognostic factors. In addition, our study suggests that ADA may also have efficacy in treating POR of CD, although from our results it seems that it is more effective in preventing than treating POR of CD. However, this may be due to the small number of patients in our cohort (Group I) and that all patients in Group II had already failed treatment with IFX and/or AZA pre-operatively which may have rendered these patients less responsive to ADA treatment.

Limitations of this study were the small number of patients, the lack of a placebo arm and blind randomization, and inability to measure trough levels of and antibodies to ADA (ATAs). However, this was a pilot study on a more homogenous cohort of patients, since these patients were followed and treated in a single center that reflects real life conditions. We believe, although trough levels of and antibodies to anti-TNFa biologics cannot explain all cases of loss of response to biologics, that time has come these measurement of antibodies and trough levels of IFX and ADA to be incorporated in routine clinical practice to optimize treatment. This is especially true for ADA because dosing regimens and treatment optimization are more 'empirical' than with IFX. Unfortunately, excessive cost and limited availability have prevented us and many other physicians to currently apply these methods routinely. To our knowledge only one study has systematically used trough levels of ADA and ATAs to assess efficacy of therapy.[33] Thus, large scale prospective, multi-center, randomized, controlled studies are awaited in order to optimize strategies for individual patients at risk for POR and assess the timing, dosing and benefits of any concomitant therapy. These studies should also incorporate non-interventional genetic, serologic, imaging, and/or other markers to identify timely CD patients at high risk for POR who may be eligible for early aggressive therapy with a biologic agent with or without an immunomodulator and/or an anti-TNFa agent as well as incorporate measurements of trough levels of ADA and ATAs to follow and optimize timely long-term treatment.[34–37]

In conclusion, in this pilot study, ADA was proved safe and effective at preventing the rate of POR in patients at high-risk for early POR as well as in reducing the clinical and

endoscopic activities in CD patients with POR who had pre-operatively failed any other available treatment, including IFX.

Conflict of interest

The authors have no conflict of interest.

Acknowledgments

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References

1. Swoger JM, Regueiro M. Preventive therapy in postoperative Crohn's disease. *Curr Opin Gastroenterol* 2010;**26**:337–43.
2. Greenstein AJ, Lachman P, Sachar DB, Springhorn J, Heimann T, Janowitz HD, et al. Perforating and non-perforating indications for repeated operations in Crohn's disease: evidence for two clinical forms. *Gut* 1988;**29**:588–92.
3. Sachar DB, Lemmer E, Ibrahim C, Edden Y, Ullman T, Ciardulo J, et al. Recurrence Patterns after first resection for stricturing or penetrating Crohn's disease. *Inflamm Bowel Dis* 2009;**15**:1071–5.
4. D'Haens G, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology* 1998;**114**:262–7.
5. Rutgeerts P, Hiele M, Geboes K, Peeters M, Penninckx F, Aerts R, et al. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* 1995;**108**:1617–21.
6. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990;**99**:956–63.
7. Olaison G, Smedh K, Sjödahl R. Natural course of Crohn's disease after ileocolonic resection: endoscopically visualized ileal ulcers preceding symptoms. *Gut* 1992;**33**:331–5.
8. Regueiro M, Kip KE, Schraut W, Baidoo L, Sepulveda AR, Pesci M, et al. Crohn's disease activity index does not correlate with endoscopic recurrence one year after ileocolonic resection. *Inflamm Bowel Dis* 2011;**17**:118–26.
9. Terdiman JP. Prevention of postoperative recurrence in Crohn's disease. *Clin Gastroenterol Hepatol* 2008;**6**:616–20.
10. Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *JCC* 2010;**4**:28–62.
11. Greenberg GR, Feagan BG, Martin F, Sutherland LR, Thomson AB, Williams CN, et al. Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled, dose-ranging study. Canadian Inflammatory Bowel Disease Study Group. *Gastroenterology* 1996;**110**:45–51.
12. Hellers G, Cortot A, Jewell D, Leijonmarck CE, Löfberg R, Malchow H, et al. Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. *Gastroenterology* 1999;**116**:294–300.
13. Lochs H, Mayer M, Fleig W, Mortensen PB, Bauer P, Genser D, et al. Prophylaxis of postoperative relapse in Crohn's disease with mesalamine: European Cooperative Crohn's Disease Study VI. *Gastroenterology* 2000;**118**:264–73.
14. Rutgeerts P, Van Assche G, Vermeire S, D'Haens G, Baert F, Noman M, et al. Ornidazole for prophylaxis of postoperative Crohn's disease recurrence: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2005;**128**:856–61.
15. D'Haens GR, Vermeire S, Van Assche G, Noman M, Aerden I, Van Olmen G, et al. Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: a controlled randomized trial. *Gastroenterology* 2008;**135**:1123–9.
16. Hanauer SB, Korelitz BI, Rutgeerts P, Peppercorn MA, Thisted RA, Cohen RD, et al. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology* 2004;**127**:723–9.
17. Reinisch W, Angelberger S, Petritsch W, Shonova O, Lukas M, Bar-Meir S, et al. International AZT-2 Study Group. Azathioprine versus mesalazine for prevention of postoperative clinical recurrence in patients with Crohn's disease with endoscopic recurrence: efficacy and safety results of a randomised, double-blind, double-dummy, multicentre trial. *Gut* 2010;**59**:752–9.
18. Papay P, Reinisch W, Ho E, Gratzer C, Lissner D, Herkner H, et al. The impact of thiopurines on the risk of surgical recurrence in patients with Crohn's disease after first intestinal surgery. *Am J Gastroenterol* 2010;**105**:1158–64.
19. Ardizzone S, Maconi G, Sampietro GM, Russo A, Radice E, Colombo E, et al. Azathioprine and mesalamine for the prevention of relapse after conservative surgery for Crohn's disease. *Gastroenterology* 2005;**127**:730–40.
20. Domenech E, Manosa M, Bernal I, Garcia-Planella E, Cabré E, Piñol M, et al. Impact of azathioprine on the prevention of postoperative Crohn's disease recurrence: results of a prospective, observational, long-term follow-up study. *Inflamm Bowel Dis* 2008;**14**:508–13.
21. Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. *Gastroenterology* 2009;**136**:441–50.
22. Yamamoto T, Umegae S, Matsumoto K. Impact of infliximab therapy after early endoscopic recurrence following ileocolonic resection of Crohn's disease: a prospective pilot study. *Inflamm Bowel Dis* 2009;**15**:1460–6.
23. Sorrentino D, Terrosu G, Avellini C, Maiero S. Infliximab with low-dose methotrexate for prevention of postsurgical recurrence of ileocolonic Crohn disease. *Arch Intern Med* 2007;**167**:1804–7.
24. Fernandez-Blanco I, Monturiol J, Martinez B, Cara C, Taxonera C. Adalimumab in the prevention of postoperative recurrence of Crohn's disease. *Gastroenterology* 2010;**138**(Suppl 1):S692.
25. Harvey R, Bradshaw J. A simple index of Crohn's-disease activity. *Lancet* 1980;**1**:514.
26. Sandborn WJ, Feagan BG, Hanauer SB, Lochs H, Löfberg R, Modigliani R, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology* 2002;**122**:512–30.
27. Sorrentino D, Paviotti A. Postoperative recurrence of Crohn's disease: the beginning of the end? *Gastroenterology* 2009;**137**:1181–2.
28. Sinagra E, Renna S, Mocciaro F, Olivo M, Cottone M, Orlando A. Early postoperative recurrence of severe Crohn's disease, with colonic involvement and associated human cytomegalovirus infection, treated with oral valganciclovir and adalimumab. *Inflamm Bowel Dis* 2011;**17**:43–4.
29. Sorrentino D, Paviotti A, Terrosu G, Avellini C, Geraci M, Zarifi D. Low-dose maintenance therapy with infliximab prevents

postsurgical recurrence of Crohn's disease. *Clin Gastroenterol Hepatol* 2010;**8**:591–9.
30. Regueiro M, Schraut WH, Baidoo L, Kip Kevin, Plevy Scott E, El-Hachem Sandra, et al. Two year follow-up of patients enrolled in the randomized controlled trial (RCT) of infliximab (IFX) for prevention of recurrent Crohn's disease (CD). *Gastroenterology* 2009;**136**(Suppl 1):A-522.
31. Biancone L, Cretella M, Tosti C, Palmieri G, Petruzziello C, Geremia A, et al. Local injection of infliximab in the postoperative recurrence of Crohn's disease. *Gastrointest Endosc* 2006;**63**:486–92.
32. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;**362**:1383–95.
33. Karmiris K, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology* 2009;**137**:1628–40.
34. Koilakou S, Sailer J, Peloschek P, Ferlitsch A, Vogelsang H, Miehsler W, et al. Endoscopy and MR enteroclysis: equivalent tools in predicting clinical recurrence in patients with Crohn's disease after ileocolic resection. *Inflamm Bowel Dis* 2010;**16**: 198–203.
35. Maconi G, Colombo E, Sampietro GM, Lamboglia F, D'Incà R, Daperno M, et al. CARD15 gene variants and risk of reoperation in Crohn's disease patients. *Am J Gastroenterol* 2009;**104**: 2483–91.
36. Maconi G, Sampietro GM, Cristaldi M, Danelli PG, Russo A, Bianchi Porro G, et al. Preoperative characteristics and postoperative behavior of bowel wall on risk of recurrence after conservative surgery in Crohn's disease a prospective study. *Ann Surg* 2001;**233**:345–52.
37. Meresse B, Rutgeerts P, Malchow H, Dubucquoi S, Dessaint JP, Cohard M, et al. Low ileal interleukin 10 concentrations are predictive of endoscopic recurrence in patients with Crohn's disease. *Gut* 2002;**50**:25–8.