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BRIEF ARTICLE

Adalimumab in prevention of postoperative recurrence of Crohn's disease in high-risk patients

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Abstract

AIM: To evaluate the effectiveness of adalimumab in preventing recurrence after intestinal resection for Crohn's disease in high-risk patients.

METHODS: A multicenter, prospective, observational study was conducted from June 2009 until June 2010. We consecutively included high-risk Crohn's disease patients who had undergone an ileal/ileocolonic resection. High-risk patients were defined as two or more criteria: smokers, penetrating pattern, one or more previous surgical resections or prior extensive resection. Subcutaneous adalimumab was administered 2 wk (± 5 d) after surgery at a dose of 40 mg eow, with an initial induction dose of 160/80 mg at weeks 0 and 2. Demographic data, previous and concomitant treatments (antibiotics, 5-aminosalicylates, corticosteroids, immunomodulators or biologic therapies), smoking status at the time of diagnosis and after the index operation and number of previous resections (type and reason for surgery) were all recorded. Biological status was assessed with C-reactive protein, erythrocyte sedimentation rate and fecal calprotectin. One year (± 3 mo) after surgery, an ileocolonoscopy and/or magnetic resonance enterography was performed. Endoscopic recurrence was defined as Rutgeerts score $\geqslant$ i2. Morphological recurrence was based on magnetic resonance (MR) score $\geqslant$ MR1.

RESULTS: Twenty-nine patients (55.2% males, 48.3% smokers at diagnosis and 13.8% after the index operation), mean age 42.3 years and mean duration of the disease 13.8 years were included in the study. A mean of 1.76 (range: 1-4) resections previous to adalimumab administration and in 37.9% was considered extensive resection. 51.7% had previously received infliximab. Immunomodulators were given concomitantly to 17.2% of patients. Four of the 29 (13.7%) developed clinical recurrence, 6/29 (20.7%) endoscopic recurrence and 7/19 (36.8%) morphological recurrence after 1-year. All patients with clinical recurrence showed endoscopic and morphological recurrence. A high degree of concordance was found between clinical-endoscopic recurrence (κ = 0.76, P < 0.001) and clinical-morphological recurrence (κ = 0.63, P = 0.003). Correlation between endoscopic and radiological findings was good (comparing the 5-point Rutgeerts score with the 4-point MR score, a score of i4 was classified as MR3, i3 as MR2, and i2-i1 as MR1) (P < 0.001, r_s = 0.825). During follow-up, five (17.2%) patients needed adalimumab dose intensification (40 mg/wk); Mean time to intensi-

fication after the introduction of adalimumab treatment was 8 mo (range: 5 to 11 mo). In three cases (10.3%), a biological change was needed due to a worsening of the disease after the dose intensification to 40 mg/wk. One patient suffered an adverse event.

CONCLUSION: Adalimumab seems to be effective and safe in preventing postoperative recurrence in a selected group of patients who had undergone an intestinal resection for their CD.

Key words: Crohn's disease; Postoperative recurrence; Prevention; Tumor necrosis factor alpha agents; Adalimumab

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INTRODUCTION

Crohn's disease (CD) is a complex chronic inflammatory bowel disease with an unpredictable course, in most cases accompanied by periodic recurrence and exacerbations[1]. Up to 70% of patients with CD have to undergo surgery due to complications of the disease at least once in their lifetime, frequently resulting in ileocolonic anastomosis[2,3]. Unfortunately, postsurgical recurrence, defined as the appearance of new lesions detected endoscopically, radiologically or pathologically, is common after surgery. One year after intestinal resection, 70%-90% of patients have endoscopic evidence of recurrent disease in the neo-terminal ileum. Despite the high endoscopic recurrence rate, symptomatic recurrence is delayed, with only 20% of patients having symptoms within the first year, increasing to one third after 3 years[4].

Ileocolonoscopy was considered the gold standard in the evaluation of postoperative recurrence, being a useful tool to predict clinical recurrence, CD-related complications and the need for repeat surgery in the future. Rutgeerts *et al*[4] devised a 5-point score ranging from i0 to i4 to measure the presence and severity of endoscopic lesions in the neoterminal ileum and anastomosis and reported a correlation between endoscopic recurrence and the likelihood of clinical recurrence, especially in those patients with more severe (i3-i4) endoscopic score.

The main limitations of ileocolonoscopy are its restriction to the level of intestinal mucosa and to the colon and neoterminal ileum area due to stenosis at the ileocolonic anastomosis site. Recently, magnetic resonance (MR) enteroclysis, a safe and non-invasive new imaging technique for small bowel, has proven to be a useful tool for detecting unsuspected penetrating disease, reaching areas restricted to ileocolonoscopy. A 4-point MR-enteroclysis-based score (MR0-MR3) has been validated by Sailer *et al*[5] and studies comparing ileocolonoscopy and MR enteroclysis suggest that they are of similar value in terms of predicting the risk of clinical recurrence in postoperative CD patients[6].

Different studies have assessed the efficacy of the available medications in the prevention of postoperative CD recurrence. Mesalamine, nitroimidazole antibiotics, azathioprine and 6-mercaptopurine have been reported to be effective treatments but have shown limited efficacy in reducing postoperative recurrence[7-12]. Recent results from a randomized placebo-controlled trial and a prospective pilot study with the chimeric anti-tumor necrosis factor alpha (TNF-α) antibody infliximab (IFX) support the utility of biologic therapies for the prevention of postoperative CD recurrence[13-15].

Adalimumab is a fully human anti-TNF-α monoclonal antibody that has been shown to be highly effective in inducing and maintaining remission in patients with moderate-to-severe CD. Adalimumab is effective not only in naïve patients but also in patients with loss of response or intolerance to IFX[16-19]. However, its efficacy in preventing postoperative recurrence has yet to be assessed.

The aim of this study is to evaluate the effectiveness and safety of adalimumab in preventing endoscopic and morphological recurrence at 12 mo after intestinal resection for CD in patients at high risk of recurrence, as well as to assess the influence of different risk factors associated with recurrence in CD patients treated with adalimumab. Additionally, we investigated the effectiveness of adalimumab in preventing clinical CD recurrence 1 year after surgery and compared endoscopic and radiological findings for predicting clinical recurrence in CD patients who had undergone intestinal resection.

MATERIALS AND METHODS

Study design

A multicenter, prospective, observational study was conducted in order to assess the effectiveness and safety of adalimumab in the prevention of postoperative recurrence of CD in high-risk patients. Four Spanish referral hospitals participated in the study.

Patients

All patients undergoing intestinal resection (macroscopically normal lines of resection) for ileal or ileocolonic CD from June 2009 to June 2010 were assessed and invited to participate. Inclusion criteria were: (1) patients aged between 15 and 70 years; (2) undergoing intestinal resection for CD; (3) high risk of recurrence, defined as at least two of the following criteria: smoker; penetrating pattern; prior extensive resection (> 100 cm); or one

or more previous surgical resections; (4) monitored for at least 1 year; and (5) if on concomitant treatments, a stable dose 12 wk before surgery and constant throughout the duration of the study. Exclusion criteria included the following: (1) patients with active ileocolonic or anorectal disease at entry; (2) more than 10 years of CD requiring first respective intestinal surgery for short (< 10 cm) fibrostenotic stricture; and (3) prior adverse events related to adalimumab.

Demographic data (gender and age), previous and concomitant treatments (antibiotics, 5-aminosalicylates, corticosteroids, immunomodulators or biologic therapies), smoking status at the time of diagnosis and after the index operation and number of previous resections (type and reason for surgery) were all recorded. Clinical data and inflammatory parameters C-reactive protein (CRP) (level in milligrams per liter), erythrocyte sedimentation rate (level in millimeters per hour) and fecal calprotectin (level in micrograms per gram) were evaluated at each visit (months 0, 3, 6, 9 and 12 after surgery). Ileocolonoscopy and magnetic resonance enterography (MRE), if available at the site, were performed at one year (± 3 mo) after treatment initiation, or withdrawal if clinical recurrence was suspected by the clinician, with or without elevated biological parameters. Adalimumab was administered 2 wk (± 5 d) after surgery with an induction dose of 160/80 mg at weeks 0 and 2 and at a maintenance dose of 40 mg subcutaneous eow. During follow-up, if at the discretion of the physician, the patient required intensified treatment, the adalimumab was increased to 40 mg every week.

Definitions

Index operation was defined as the last ileal or ileocolonic resection prior to the study. Baseline data, month 0, refers to the month when the index operation was performed. Clinical postoperative recurrence was defined as the onset of symptoms (diarrhea, abdominal pain and decreased well-being) or complications that led to changes in medical or surgical management.

Endoscopic recurrence refers to the existence of new mucosal (endoscopic) lesions in the neoterminal ileum after surgery. Ileocolonoscopy was performed by an experienced endoscopist and classified according to Rutgeerts score[4] (Table 1). Endoscopic recurrence was defined as i2-i4 classified endoscopic findings.

Morphological recurrence refers to the occurrence of new lesions assessed by imaging techniques. MRE was performed with administration of oral contrast (1500 mL of 5% mannitol solution) as described Leyendecker *et al*[20]. The presence of irregularities in mucosal surface, enhancement of mucosal contrast, thickening of the bowel wall, stenosis and extramural abnormalities (abscesses and fistulas) were evaluated and MRE findings were classified into the four grade MR score (Table 1)[5]. Morphological recurrence was defined as MR1-MR3 classified MRE findings. Radiologist and endoscopist were blinded to the results of each other and to the inflammatory marker testing to assure correct and non-biased results.

Statistical analysis

Continuous variables were summarized as mean ± SD or range when appropriate. Test of normality was developed using the D'Agostino test. Categorical variables were summarized as frequencies and percentages. Concordance between clinical-endoscopic recurrence and clinical-morphological recurrence was calculated with the weighted kappa statistic (κ). Kappa values were interpreted as follows: 0.99-0.81 "almost perfect agreement"; 0.80-0.61 "substantial agreement"; 0.60-0.41 "moderate agreement"; 0.40-0.21 "fair agreement" and less than 0.2 "slight agreement"[21]. Correlation between endoscopic and morphological recurrence was calculated using Spearman rank correlation. Univariate logistic regression was performed to assess the influence of variables collected on the development of recurrence. Logistic regression multivariate analysis could not be performed due to the low number of observations. Differences were considered significant if P value < 0.05.

RESULTS

Demographics and clinical history

Twenty-nine patients were included in the study, 16 (55.2%) of whom were male. Mean age at diagnosis of CD was 28 years (range: 13-60 years). Demographic and clinical characteristics are shown in Table 2. The mean time from diagnosis to the last resection was 166 mo (range: 7 to 365 mo). Mean age at the last resection was 42.3 ± 11.18 years. The indication for resection was therapeutic failure in 10/29 (34.5%), stenosis in 17/29 (58.6%) and penetrating pattern in 2 (6.9%) cases. Almost all patients (28 of 29) had been treated with a course of systemic corticosteroids at some point for the disease (mean No. courses: 5.7; range: 1-10) and 12 (42.9%) had received corticosteroids prior to the index operation. In addition, 41.4% of patients were taking antibiotics at the time of the index operation. IFX had been taken previously by 15 (51.7%) patients and aminosalicylates by 13 (44.8%) patients. Concomitant treatment with thiopurines was given to five (17.2%) patients and enteral nutrition therapy (elemental and/or semi-elemental formulas) in six (20.7%) patients. Patients' smoking status, at diagnosis and after the index operation was evaluated. At diagnosis, almost half (48.3%) were smokers while after the index operation, only 4 (13.8%) continued smoking.

Adalimumab intervention

All patients were treated with an induction dose of 160/80 mg subcutaneous adalimumab at weeks 0 and 2 and at a maintenance dose of 40 mg eow after intestinal resection. During follow-up, colonoscopy and MRE were necessary to continue in five (17.2%) patients because of suspected clinical recurrence and/or elevated

Table 1 Rutgeerts and magnetic resonance score for classification of postoperative recurrence in Crohn's disease

Rutgeerts score	Description	MR score	Description
i0	No lesions	MR0	No findings
i1	Less than 5 aphthous lesions	MR1	Minor mucosal irregularities: Slight wall thickening Slight mural contrast enhancement No stenosis
i2	More than 5 aphthous lesions with normal mucosa between the lesions or skip areas or larger lesions or lesions confined to ileo-colonic anastomosis		
i3	Diffuse aphthous ileitis with diffusely-inflamed mucosa	MR2	Major mucosal abnormalities: Distinct bowel wall thickening Distinct mural contrast enhancement Low grade stenosis without prestenotic dilatation
i4	Diffuse inflammation with already large ulcers, nodules and/or narrowing	MR3	Same finding as MR 2 plus: Transmural edema with T2w signal increase and contrast enhancement of the perienteric fat High grade stenosis without prestenotic dilatation Extramural complications (fistula, abscess, conglomeration of bowel loops)

MR: Magnetic resonance; MR0-MR3: A 4-point MR-enteroclysis-based score; i0-i4: A 5-point score to measure the presence and severity of endoscopic lesions in the neoterminal ileum and anastomosis.

Table 2 Patient characteristics at baseline (*n* = 29) (%)

Patient characteristics	Value
Gender	
Female	13 (44.8)
Age (yr), mean (range)	42.3 (19.8-61.1)
Duration of the disease (mo), median (range)	166 (7-365)
Montreal classification:	
A1 (< 17 yr)	6 (20.7)
A2 (17-40 yr)	17 (58.6)
A3 (> 40 yr)	6 (20.7)
L1 (ileal)	15 (51.7)
L3 (ileocolonic)	9 (31.0)
L1 + L4 (ileal + upper gastrointestinal)	5 (17.2)
B1 (non-stricturing/penetrating)	9 (31.0)
B2 (stricturing)	14 (48.3)
B3 (penetrating)	6 (20.6)
Perianal disease	10 (34.4)
Extensive resection	11 (37.9)
Immunomodulators (AZA, 6-MP) concomitant to adalimumab	5 (17.2)
Concomitant enteral nutrition	6 (20.7)
Previous infliximab	15 (51.7)
Previous resections (including index operation)	
1	15 (51.7)
2	7 (24.1)
3	6 (20.7)
4	1 (3.4)
Smoking status at diagnosis	
Smokers	14 (48.3)
Ex-smokers	2 (6.9)
Non-smokers	13 (44.8)
Smoking status after the index operation	
Smokers	4 (13.8)
Ex-smokers	12 (41.4)
Non-smokers	13 (44.8)

AZA: Azathioprine; 6-MP: 6-mercaptopurine.

biological parameters. All patients had endoscopic and morphological recurrence and needed adalimumab dose intensification (40 mg every week). Mean time to intensification after the introduction of adalimumab treatment was 8 mo (range: 5 to 11 mo). The 5 patients had received thiopurine drugs and 4 of them, biological treatment with IFX, before index surgery. Concomitant treatment with immunomodulators was given to one of the 5 patients.

In three cases (10.3%), a biological change was needed due to the persistence of symptoms and progressive elevation of acute-phase reactants after the dose had been increased to 40 mg every week. Two of the three patients had previously received IFX and changed to certolizumab, and the third had switched to IFX.

Primary endpoint: Endoscopic and morphological recurrence at 12 mo

Six of the 29 (20.7%) showed endoscopic recurrence (i2-i4). Two patients had an endoscopic grade score of i2, two patients had a score of i3 and the other two, i4. Additionally, 19 of the 29 (65.5%) patients had MRE 1 year after resection. In 7 of the 19 (36.8%), morphological recurrence (MR1-MR3) was observed. Three had an MR score of MR1, three of MR2 and the other patient, MR3 (Table 3).

Influence of clinical parameters in endoscopic recurrence: In the univariate analysis (Table 4), two variables were found to be associated with endoscopic recurrence. Patients with extensive resection (over 100 cm) [odds ratio (OR): 14.17, 95% CI: 1.12-708.0, $P = 0.026$] and with more than two previous resections (OR: 13.3, 95% CI: 1.7-107.4, $P = 0.015$) had increased risk of endoscopic recurrence. Other variables studied, such as the disease pattern, presence of perianal disease, number of previous surgical resections, indication of surgery and IFX treatment failure had no significant influence on the endoscopic recurrence rate.

Table 3 Correlation between endoscopic and radiological findings *n* (%)

Rutgeerts score	MR score			
	MR0	MR1	MR2	MR3
i0	9 (100)	0	0	0
i1	3 (75)	1 (25)	0	0
i2	0	1 (50)	1 (50)	0
i3	0	1 (50)	1 (50)	0
i4	0	0	1 (50)	1 (50)

MR: Magnetic resonance; MR0-MR3: A 4-point MR-enteroclysis-based score; i0-i4: A 5-point score to measure the presence and severity of endoscopic lesions in the neoterminal ileum and anastomosis.

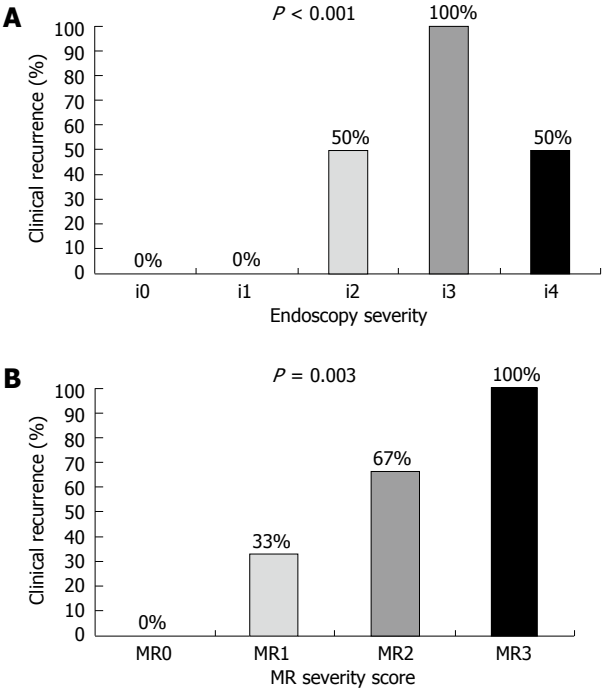

Figure 1 Concordance after ileocolonic resection for Crohn's disease. A: Between clinical-endoscopic recurrence; B: Between clinical-morphological recurrence. MR: Magnetic resonance; MR0-MR3: A 4-point MR-enteroclysis-based score; i0-i4: A 5-point score to measure the presence and severity of endoscopic lesions in the neoterminal ileum and anastomosis.

Table 4 Univariate analysis for endoscopic recurrence *n* (%)

Endoscopic recurrence		Yes	No	*P* value
Gender	Female	3 (23.1)	10 (76.9)	0.775
	Male	3 (18.8)	13 (81.3)	
Duration of the disease	≤ 10 yr	3 (23.1)	10 (76.9)	0.775
	> 10 yr	3 (18.8)	13 (81.3)	
Pattern	Non-stricturing, non-penetrating	2 (22.2)	7 (77.8)	0.318
	Stricturing	4 (28.6)	10 (71.4)	
	Penetrating	0 (0)	6 (100)	
Extensive resection	Yes	5 (45.5)	6 (54.5)	0.026
	No	1 (5.6)	17 (94.4)	
Immunomodulators concomitant to ADA	Yes	1 (20)	4 (80)	0.967
	No	5 (20.8)	19 (79.2)	
Prior infliximab	Yes	5 (33.3)	10 (66.7)	0.111
	No	1 (7.1)	13 (92.9)	
Previous resections	≤ 2	2 (9.1)	20 (90.9)	0.015
	> 2	4 (57.1)	3 (42.9)	
Smoking status at diagnosis	Smokers	3 (21.4)	11 (78.6)	0.516
	Non-smokers	3 (23.1)	10 (76.9)	
	Ex-smokers	0 (0)	2 (100)	
Smoking status after the index operation	Smokers	2 (50)	2 (50)	0.119
	Non-smokers	4 (16)	21 (84)	
Adverse events	Yes	0 (0)	1 (100)	0.454
	No	6 (22.2)	21 (77.8)	

ADA: Adalimumab.

Secondary endpoints

Clinical recurrence at 12 mo: Four of the 29 (13.7%) patients developed clinical recurrence 1 year after intestinal surgery. In the univariate analysis, active smoker status after the index operation was significantly correlated with higher clinical recurrence rate (smokers *vs* non-smokers OR: 11.50; 95% CI: 1.01-131.29; $P = 0.049$). Patients with extensive resection (OR: 14.17; 95% CI: 1.12-708.0; $P = 0.014$) were significantly correlated with the development of clinical recurrence. No other significant correlations were found with the other variables.

Correlation between clinical, endoscopic and morphological recurrence: After 12 mo of follow-up, all patients with clinical recurrence (four patients) showed endoscopic and morphological recurrence. Patients with clinical recurrence were classified into i2-i4 groups (1 in i2, 2 in i3 and 1 in i4) using the Rutgeerts score for Postoperative Endoscopic Classification of CD[4]. There was significant concordance (substantial agreement) between the endoscopy severity and the clinical recurrence rate ($\kappa = 0.76$, $P < 0.001$) (Figure 1A).

Similarly, with the MR score, the four patients with clinical recurrence showed radiological recurrence (1 in MR1, 2 in MR2 and 1 in MR3). Also, substantial agreement between MR-score severity and the clinical recurrence rate was observed ($\kappa = 0.63$, $P = 0.003$) (Figure 1B).

Endoscopic and MRE evaluation was possible in 19 patients. Correlation between endoscopic and radiological findings was good. The Spearman rank correlation coefficient between the two techniques was $r_s = 0.889$ ($P < 0.001$) when dichotomous outcome "recurrence, yes or no" was correlated. To compare the 5-point Rutgeerts score with the 4-point MR score, a score of i4 was classified as an MR score of MR3, i3 was defined as equivalent to MR2, and i2-i1 were classified as MR1, consistent with the fact that MR imaging does not provide sufficient spatial resolution to differ between i1 and i2[6]. In this case, the Spearman rank correlation coefficient was $r_s = 0.825$, $P < 0.001$.

Using endoscopy as the gold standard, the sensitivity of MRE for detecting moderate-to-severe endoscopic findings (Rutgeerts score i3 and i4) was 75%; specificity 93.3%, positive predictive value 75% and negative predictive value 93.3%.

Safety: One (3.4%) patient reported an adverse event during the 12 mo of follow-up: episodes of peripheral

vertigo. Although the etiology for this adverse event was not identified, adalimumab treatment was discontinued at month 6. This patient continued without treatment and remained in remission at month 12.

Ethical considerations

The study was carried out in accordance with the Declaration of Helsinki principles of good clinical practice. The study protocol was reviewed and approved by the local independent ethics committee.

DISCUSSION

In this study, we found adalimumab to be effective and safe in preventing recurrence after surgery for CD in a special subgroup of patients at high risk of recurrence. Intestinal resection is not curative and the majority of patients develop endoscopic recurrence even before clinical symptoms become apparent. Early detection and treatment of endoscopic lesions is essential to improve the long-term outcome for these patients and thus, to improve their quality of life. One year after intestinal resection, 70%-90% of patients have endoscopic recurrence and clinical recurrence occurs in nearly 20%[4]. A number of studies have evaluated the efficacy of active treatment (mesalamine, nitroimidazole antibiotics and immunomodulators) for prevention of postoperative CD recurrence and most of them reported endoscopic recurrence to be between 40% and 60% at 12 mo after surgery[22]. Recently, the anti-TNF-α antibody, IFX, has been associated with a significant reduction in postoperative recurrence in CD[14,15,23,24]. However, to date, there have been no published results with adalimumab, only a case series of six patients who underwent resection for an ileocecal stricture in which adalimumab was successfully used to prevent postsurgical recurrence of CD[25]. For this reason, we decided to evaluate the effectiveness and safety of adalimumab in preventing postoperative endoscopic and morphological recurrence as the primary study endpoint. This cohort of patients developed clinical recurrence in 13.7% of cases, endoscopic recurrence in 20.7% and MRE recurrence in 36.8%, although MRE was only evaluated in 19 patients and could be overestimated. In the clinical trial conducted by Regueiro *et al*[14], 9.1% of patients in the IFX-treated group had endoscopic recurrence and 84.6% in the placebo group. In our study, the rate of endoscopic recurrence was higher, at 24.1%. It is important to take into account that our results refer to a special subgroup of patients with high risk factors for recurrence (two or more of: smoker, penetrating pattern, prior extensive resection and one or more previous surgical resections), so higher percentages are expected. In addition, there were several differences between the two studies in terms of design. In our cohort, only 5 of the 29 patients (17.2%) were on concomitant immunomodulator treatment whereas this applied to 4 of the 11 (36.4%) patients in the IFX-treated group in the Regueiro study. Also, in the clinical trial with IFX, only one (9.1%) patient had previously undergone more than two intestinal resections compared to 7 (24.1%) patients in this study.

Different risk factors have been associated with postoperative CD recurrence. However, cigarette smoking is the only modifiable risk factor to be identified to date, and the most significant, with twice the risk of presenting a clinical recurrence compared with non-smokers[26,27]. We found an increased clinical recurrence risk in patients who reported smoking at the time of the index operation compared with non-smokers. When we evaluated patients who were smokers at the time of diagnosis, no differences in risk were found. This was consistent with other studies that found no increased risk in ex-smokers[26,27] or reported a reduction in the recurrence rate after stopping[28,29] and suggests that the effect of smoking disappears some time after giving up the habit. These results support the fact that physicians should advise, encourage and assist CD patients to stop smoking. Another factor to consider is the length of the previous intestinal resection. In our study, the clinical and endoscopic recurrence rate was higher in patients with prior extensive resection (> 100 cm) and with more than two previous resections, consistent results with those obtained from the study about the impact of azathioprine on the prevention of postoperative CD recurrence[9]. Other risk factors for postoperative CD recurrence, such as penetrating pattern, duration of CD or complex perianal disease, did not influence the proportion of patients with endoscopic and/or morphological recurrence.

Clinical postoperative recurrence was defined as the presence of symptoms, such as diarrhea, abdominal pain or decreased well-being, or complications which led to changes in medical or surgical management. All patients with clinical recurrence showed endoscopic and morphological recurrence 1 year after intestinal resection.

We avoided using the clinical activity index because it is difficult to perform in this setting. Some studies in which clinical postoperative recurrence was measured with the Crohn's Disease Activity Index did not correlate with endoscopic recurrence one year after ileocolonic resection, while inflammatory parameters, such as CRP values, showed good correlation with endoscopic recurrence at one year[30,31]. We decided to use serum and fecal biological markers because they represent objective and quantifiable estimates of inflammatory activity. The main advantages are its simplicity and reproducibility; they can be repeated frequently to monitor changes in inflammatory activity, whether spontaneous or induced by treatment. We found that two or more elevated inflammatory parameters showed good correlation with endoscopic and morphological recurrence, especially in those scores indicating more severe lesions (i3-i4 or MR2-MR3). These techniques have been compared previously and our results are consistent with available data[5,6].

The incidence of side effects (3.4%) was no different from other published series. The patient that developed

an adverse event also had to discontinue treatment with IFX previously. This is consistent with a recent study that concluded that elective switching from IFX to adalimumab may be associated with loss of tolerance within one year, and the recommendation is therefore to adhere to the first anti-TNF agent[32].

We are aware of the potential limitations of our study. The main one is that there was no control group, so we cannot accurately compare our results with those obtained in other studies such as Regueiro *et al*[14]. Secondly, the number of patients included in this cohort study was small, which may compromise statistical validity and not allow differences to be established in some of the variables measured. Lastly, five patients were treated concomitantly with immunomodulators, although there was no change in the dose regimen for these drugs before or during the study. It is difficult to assess the added benefit of co-treatment in preventing postoperative recurrence. In fact, in the Regueiro clinical trial, with a higher percentage of patients on immunomodulators, the concomitant use of immunomodulators did not appear to influence postoperative recurrence.

In summary, a significant percentage of CD patients require intestinal resection surgery over the course of their disease, and almost all show endoscopic recurrence one year after resection. This is the first published study on the effectiveness of adalimumab in preventing endoscopic and morphological recurrence after intestinal resection for CD. Our results strongly suggest that adalimumab is effective in patients with several risk factors associated with postoperative recurrence, such as smokers, penetrating pattern, or previous and extensive intestinal resections. Obviously, further randomized, controlled trials with better design and a larger number of patients are needed to confirm our conclusions and determine the duration of adalimumab maintenance treatment after surgery.

COMMENTS

Background

Crohn's disease (CD) is a complex chronic inflammatory bowel disease with an unpredictable course, in most cases accompanied by periodic recurrence and exacerbations. Up to 70% of patients with CD have to undergo surgery due to complications of the disease at least once in their lifetime, frequently resulting in ileocolonic anastomosis.

Research frontiers

Ileocolonoscopy was considered the gold standard in the evaluation of postoperative recurrence, being a useful tool to predict clinical recurrence, CD-related complications and the need for repeat surgery in the future.

Innovations and breakthroughs

A multicenter, prospective, observational study was conducted from June 2009 until June 2010. Authors consecutively included high-risk CD patients who had undergone an ileal/ileocolonic resection.

Applications

In this study, authors found adalimumab to be effective and safe in preventing recurrence after surgery for CD in a special subgroup of patients at high risk of recurrence. Intestinal resection is not curative and the majority of patients develop endoscopic recurrence even before clinical symptoms become apparent. Early detection and treatment of endoscopic lesions is essential to improve the long-term outcome for these patients and thus, to improve their quality of life.

Peer review

This manuscript is a prospective observational study that evaluated the effectiveness of adalimumab (ADA) for the prevention of postoperative recurrence of CD. Although this study lacks control group, this is the first prospective study on the efficacy of ADA for postoperative prevention of CD, so the presented data are important for the clinical practice and for the future controlled trial.

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