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Adalimumab *versus* infliximab in treating post-operative recurrence of Crohn's disease: a national cohort study

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ABSTRACT

Aim: Perform a comparison between adalimumab (ADA) and infliximab (IFX) in treating post-operative recurrence of Crohn's disease (a comparative analysis of efficacy and safety).

Methods: From the 267 patients treated with adalimumab or infliximab between January 2005 and June 2014 in Romania, 44 received anti-TNF (tumor necrosis factor) therapy for prevention of post-operative recurrence. A comparison between patients treated with IFX and ADA was made with the Chi-square and t-student test, with the aid of the statistical program Mini Tab 17.

Results: Twenty-one patients received IFX and 23 ADA. This included 49% males (22/44), with a mean age of 41 years, mean disease duration of 6 years, and 84.1% had previously received azathioprine. The IFX group is comparable with the ADA group regarding most of the parameters, except for therapy duration. Mean duration of therapy was 33 months. The rate of complete response was comparable between the two groups: 67% in the IFX group *vs.* 78.3% in the ADA group, the same as the rate of re-resection, 19.1% *vs.* 4.4% and the rate of endoscopic recurrence, 29 *vs.* 33% at 12 months. Risk factors for postoperative recurrence (POR) (male sex, younger age, ileocolonic location, stricturing or penetrating behaviour) were studied, only ileocolonic location was found to be associated with Crohn's disease recurrence in patients treated with ADA.

Conclusions: Overall infliximab and aalimumab are equally efficient in patients with resected Crohn's disease (CD) with a complete response of 72.7%, a rate of re-resection of 11.4% and a rate of endoscopic recurrence of 35%. Ileocolonic location might be a predictive factor for loss of response to adalimumab in resected Crohn's disease patients.

Key words: Adalimumab. Infliximab. Crohn's disease. Cohort study. Postoperative recurrence.

INTRODUCTION

Crohn's disease (CD) is a lifelong disease arising from an interaction between genetic and environmental factors, but predominantly observed in developed countries of the world. The precise etiology is unknown; therefore a causal therapy is not yet available (1). CD can affect the entire digestive tract from the mouth to the anus (2), but the most commonly affected sites are the ileum and the ascending colon (3). The clinical course of CD is characterized by exacerbations and remissions. Therefore recurrent inflammation can cause bowel strictures, fistulae (often perianal) or abscesses (4).

In the natural history of Crohn's disease, intestinal resection is almost unavoidable as about 80% of patients require surgery at some stage. Surgery is unfortunately not curative as the disease reoccurs in many patients (5).

Although a wide range of postoperative recurrence rates have been reported according to the definitions of recurrence (clinical, endoscopic or surgical recurrence), there is common agreement that the recurrence rate steadily increases with time, reaching approximately 50% at 20 years after surgery (4). The reported clinical postoperative recurrence rate is between 17-55% at 5 years (6). However endoscopic evidence of recurrence is present in 70%-90% patients at one year after intestinal resection (7). Endoscopic lesions usually precede and correlate with future clinical recurrence, and predict the development of Crohn's disease-related complications and the need for re-intervention. Therefore, endoscopic follow-up 6-12 months after surgery is recommended (8).

Several studies have reported potential risk factors for postoperative recurrence in CD, such us cigarette smoking (9), penetrating disease behavior (10), perianal localization (11) and previous intestinal surgery (including appendectomy) (12). All these factors have been shown to predict early post- operative recurrence (5). The identification of risk factors is an important step in the management of postoperative recurrence because it can help in the selection of patients who may benefit from prophylactic measures.

In contrast with high overall recurrence rates, the severity of recurrence varies among patients. Some of them may only develop mild endoscopic recurrence and have no

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symptoms, whereas others may present early after surgery with inflammation and clinical symptoms (13).

Medical management of Crohn's disease is a fast evolving area, with more medical treatments that have proved their effectiveness in inducing and maintaining the remission. Therefore many studies have attempted to establish whether these therapies can be effective in preventing postoperative recurrence. The results are not very consistent and many therapies have shown little benefit. Mesalamine, nitroimidazole antibiotics, thiopurine analogues (azathioprine and 6-mercaptopurine) have been reported to be effective treatments but have shown limited efficacy in reducing postoperative recurrence (14,15).

There is increasing data with regard to biological therapies, such as anti TNF alpha therapies such as infliximab (IFX), a chimeric immunoglobulin G (IgG) human (75%)/ murine (25%) administered by intravenous infusion and adalimumab (ADA) a self-injected, fully humanized recombinant monoclonal antibody (mAb). Reports state that they may be more effective than the placebo in the reduction of postoperative recurrence (16,17). Despite this fact, one recent study has shown that IFX has the same effectiveness as azathioprine in reducing endoscopic and clinical recurrence (18).

The few studies comparing ADA and IFX effectiveness have not shown large differences between the two therapies in preventing clinical, endoscopic and histological recurrence of Crohn's disease. (19) In Crohn's disease, for patients at high risk of post-operative recurrence, adalimumab is superior to thiopurines in preventing early disease recurrence (20).

The aim of our study was to evaluate whether ADA and IFX can treat POR of CD and to identify which biologic agent is more effective in a national cohort.

MATERIAL AND METHODS

Two hundred and sixty-seven patients with CD were treated with infliximab or adalimumab in a period of 9 years (January 2005-June 2014) in Romania. All the patients were biological naïve. A retrospective cohort study was performed including 44 resected patients with post-operative recurrence. The data were collected from existing patient files in the archive of the National Insurance House.

Inclusion criteria: adults or children (6 to 17 years) with moderate-severe post-operative recurrence of Crohn's disease with inadequate treatment response or intolerance to standard therapy (corticosteroids, azathioprine) or cortico-dependent and those with fistulising CD non-responsive to conventional therapy (presumed to not have an abscesses).

Patients on infliximab received induction therapy with Infliximab 5 mg/kg 0, 2, 6 weeks, followed by maintenance therapy: 5 mg/kg at 8 weeks. If the subject becomes non-responsive, the interval between the doses is shortened at 6 or 4 weeks, or the dose is doubled to 10 mg/kg at 4 weeks at the indication of his physician-gastroenterologist.

Patients on adalimumab received two induction doses (160 mg and 80 mg or 80 and 40 mg subcutaneously [sc]) at weeks 0 and 2 as well as maintenance therapy (40 mg subcutaneously every other week). At or after eight weeks, patients with flare or non-responders had their dosage increased to 40 mg subcutaneously weekly.

The diagnosis was confirmed by clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations. Patients were classified according to Montreal phenotype classification (13)

The recorded information was: type of disease, age, sex, time of disease prior to IFX or ADA therapy, and location of CD (terminal ileum and colon, colon only, or ileum/small bowel only). Smoking history was poorly recorded and therefore omitted. Laboratory data were recorded in three periods to assess changes: within 1 month prior to IFX/ADA therapy, at 6 weeks after the first infusion and then at 6 months during the maintenance period. Parameters recorded included hemoglobin, white blood cells, platelet count, mean platelet volume, lymphocyte number and percentage, polymorphonuclear leukocytes, C-reactive protein, albumin, urea, creatinine, AST, ALT, glucose level. The C reactive protein (CRP) broadly correlates with disease activity of CD assessed by standard indices and indicates serial changes in inflammatory activity because of its short half life of 19 h (16).

Relevant therapeutic data before IFX/ADA were recorded: either no therapy, either prednisone, either azathioprine. Information on the intake of medications other than IFX/ADA after the start of therapy was recorded inconsistently and was therefore omitted from the analysis. However, the type of previous surgical interventions and the presence of external fistulae were recorded, as well as side effects. The surgical interventions after the initiation of biological therapy were also recorded.

Screening for active infection and for latent tuberculosis (chest X-ray and cutaneous PPD test or Quantiferon) was performed in all patients before starting anti-TNF therapy.

The median length of follow-up was also defined by the median length of treatment. Duration of response was reflected as the period of time between the first dose (induction phase) and the last dose. Those patients continuing therapy were considered to be in remission by their physicians, so this is a marker of successful maintenance or no relapse.

Statistical analysis

Statistical analysis was performed with the Minitab Statistical Software (version 17, Minitab Inc., State College, Pennsylvania, USA). Descriptive statistics were used to summarize the data. Averages with standard deviation were calculated for continuous data and percentages were calculated for categorical data. Demographic and baseline characteristics of the groups (those who received infliximab *versus* those with adalimumab) were compared using the chi-square test or Fisher's exact test for categorical variables and the t-Student two-tailed test for continuous variables. p value < 0.05 was considered significant. The association between the demographic, clinical and laboratory parameters and response to therapy were examined by binary logistic regression due to their nature as a dichotomous response variable (response Yes or No).

RESULTS

The indication for surgical interventions was complicated CD, such as small-bowel obstruction or abscess formation due to penetrating disease. Resected patients received 48% IFX and 52% ADA. All enrolled patients were fully compliant with the treatment prescribed. As outlined in table I the two groups IFX and ADA are statistically comparable regarding: gender, mean age, severity of the disease at the initiation of therapy, location, behavior, perianal disease, disease duration. Most of the patients (84%) received Azathioprine before the anti-TNF agent 1 month after surgery and stopped 6 months later.

The two groups are not comparable with regard to therapy duration (Tables I and II).

One of the patients in ADA group underwent a re-resection for POR compared with 4 in IFX group. The difference can be explained by the longer therapy duration in the IFX group.

Just one re-intervention occurred in the ADA group: one male, aged 29, A2L1B3, who underwent 2 surgical interventions before biologic therapy: one laparotomy for intraperitoneal supuration and one enteral resection for enterovesical fistula and ileal stenosis. The patient failed to respond to Adalimumab a second time after 12 months and thus underwent surgery again: ileal resection for mul-

Table II. Duration of biologic therapy and type of response to therapy in resected patients according to group of patients

	IFX (21 patients)	*ADA (23 patients)*	*p**
Therapy duration (months) mean (Stdev)	42.5 (22.2)	20.0 (10.6)	0.001
Secondary loss of response	7 (33%)	5 (21.7%)	0.388
Complete response	14 (67%)	18 (78.3)	

Values are given as number (%) of patients, unless otherwise specified. *p values were calculated using Chi-square test Fisher's exact test for categorical variables and the t-Student test for continuous variable.

Table I. Demographic and clinical features of resected patients with Crohn's disease treated with biologicals

	IFX (21 patients)	*ADA (23 patients)*	*p**
Gender male	8 (38.1%)	14 (60.9%)	0.131
Age mean (SD)	42.1 (11.1)	39.0 (12.6%)	0.377
Severity of the disease at the initiation of therapy			
Mild	2 (9.5%)	4 (17.3%)	0.447
Moderate	18 (85.7%)	19 (82.6%)	
Severe	1 (4.7%)	0	
A1 (< 17 yr)	0	1 (3.5%)	0.570
A2 (17-40 yr)	13 (61.9%)	15 (65.2%)	
A3 (> 40 yr)	8 (38.1%)	7 (30.4%)	
L1 (ileal)	3 (14.3%)	6 (26.0%)	0.606
L2 (colonic)	6 (28.5%)	5 (21.7%)	
L3 (ileocolonic)	12 (57.1%)	12 (52.1%)	
B1 (non-stricturing/penetrating)	4 (19.1%)	3 (13.1%)	0.148
B2 (stricturing)	5 (23.8%)	12 (52.1%)	
B3 (penetrating)	12 (57.1%)	8 (34.8%)	
Perianal disease	4 (19.1%)	3 (13.1%)	0.586
Patients re-resected under biologics	4 (19.1%)	1 (4.4 %)	0.115
Azathioprine (Y)	18 (85.7%)	19 (82.7%)	0.778
Positive initial TST/IGRA	7 (33.3%)	3 (13.1%)	0.126
Disease duration (years) mean (SD) at the initiation of the therapy	6.33 (5.56)	5.47 (6.93)	0.670
Initial CRP (mean ± SD)	31.7 ± 57.9	30.5 ± 46.5	0.943
CRP at the last visit (mean ± SD)	3.29 ± 5.1	10.3 ± 24.0	0.226
Period of time between surgery and biologic initiation (months) (mean ± SD)	49.1 ± 38.2	41.4 ± 43.5	0.562

Values are given as number (%) of patients. *p values were calculated using Chi-square test or Fisher's exact test for categorical variables and the t-student test for continuous variables. IFX: infliximab; ADA: adalimumab; IDR: intradermic reaction; CRP: C reactive protein.

tiple ileocolonic fistulas, ADA therapy was reinitiated with a good response and clinical remission.

Four patients in IFX needed to be re-operated: 4 males, age 25-56 years, three A2L3B3, one A3L2 B3. Two patients underwent re-resection for multiple entero-cutaneous fistulas, and the other two for sigmoid stenosis, and ileal stenosis respectively. Time to re-intervention was 12 months in two cases since IFX initiation, and 15 months in one patient and 19 months in the other case.

Ileocolonoscopy with biopsies was performed after 12 months of therapy in 27 patients.

At 12 months, 4/14 (28.6%) of the patients treated with IFX had endoscopic recurrence (Rutgeerts' score i2-i4) compared to 4/12 (33 %) patients in the ADA group (p = NS).

At the end of the study, there was no significant difference in the median CRP level in the two groups: 3.29 ± 5.1 mg/L (mean range) in patients treated with IFX compared to 10.3 ± 24.0 mg/L (mean range) in the ADA group (p = 0.226).

Table II presents the type of response to biologic therapy in the two groups of patients: infliximab and adalimumab are equally effective in inducing complete response (i.e remission in long term follow-up). The difference regarding the rate of secondary loss of response (33% in Infliximab treated patients *versus* 22% in adalimumab treated patients) can be explained by the longer therapy duration in the IFX group.

Even in non-resected patients included in our cohort of 267 subjects, the risk of surgical interventions on biologic therapy was 6%.

Because the two groups of patients are not entirely statistically comparable, figure 1 describes the proportion of patients who maintain the clinical remission over time.

Risk factors for postoperative recurrence were studied, and none was found to be statistically signifficant in patients treated with infliximab (Table III). Failure to find predictive factors for disease recurrence might be a consequence of a relatively small sample size. The situation is different in those treated with adalimumab because all patients recorded clinical recurrence (5) with L3 location (but this might be by chance, not necessarily statistically significant, so we were not able to calculate OR). Male sex or disease behavior does not predict POR also in patients treated with adalimumab (Table IV). Regarding age in this sub-group of patients, they are approximately equally distributed between the age sub-groups: 2 A2, 2 A3, 1 A1.

Adverse events in the two groups were studied: one patient aged 60 in the IFX group developed a severe allergic reaction after 3 infusions, was switched to ADA and died after 16 months of biologic therapy because of a stroke (she also suffered from severe hypertension).

In ADA group, one male aged 44 reported joint pain and a cutaneous rash, which lead to a cesation of therapy.

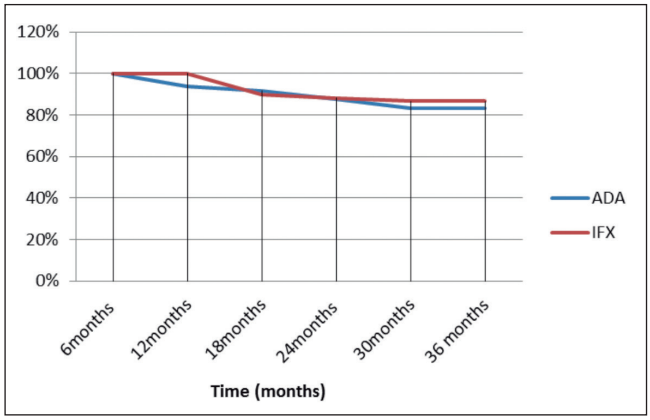

Fig. 1. Rate of complete response over time to biologic therapy in resected patients treated with adalimumab/infliximab.

DISCUSSION

Postoperative recurrence is observed in a high proportion of CD patients after resection, reaching 79% after 6 years of follow-up (12). Risk factors for postoperative recurrence in Crohn's disease are considered to be: active smoking, penetrating behavior, perianal lesions, prior intestinal resection, extensive small bowel disease (5,6,11).

In the study of Aguas M et al., 29 resected patients with CD were prospectively followed for one year after surgery while on adalimumab therapy. Duration of the disease after biologic therapy initiation in their cohort was significantly greater (13.8 years) compared to our cohort which was 6 years. A 13.7% of their patients developed clinical recurrence and 20.7% endoscopic recurrence, which is similar to our results. A second surgery was reported in this Aguas group, but in our cohort one re-resection was necessary after

Table III. Predictive factors for POR in resected patients treated with IFX

	OR	*95% CI*	*p-value*
Male sex	1.35	0.21, 2.28	0.751
Younger age	1.35	0.22, 5.61	0.750
Ileocolonic location	1.42	0.15, 2.34	0.547
Stricturing or penetrating behaviour	0.33	0.03, 2.83	0.618

Table IV. Predictive factors for POR in resected patients treated with ADA

	OR	*95% CI*	*p-value*
Male sex	0.33	0.05, 2.56	0.285
Stricturing or penetrating behaviour	0.66	0.03, 2.41	0.797

12 months of biologic therapy. In the univariate analysis, active smoker status after the index operation and extensive resection were significantly correlated with a higher clinical recurrence rate. Unfortunately, we did not have data regarding smoking status and extensive intestinal resection (more than 100 cm). No other significant correlations were found with the other variables, consistant with our study (17).

In our study we found a high rate of complete response under treatment with IFX or ADA in patients who underwent surgical resection and a loss of response rate comparable between the two groups.

Note that 13 patients out of 216 who had not undergone a resection prior to biological treatment underwent surgery during treatment (6%). Four out of the 21 patients treated with IFX underwent re-resection whereas only 1 of the 28 patients treated with ADA underwent surgical re-intervention, but the difference may be explained by the longer period of time during which the patients were treated in the IFX group.

Most studies from the literature are addressing the issue regarding the prevention of post-operative recurrence in Crohn's disease. Regarding infliximab, Regueiro et al. showed in their study (a prospective, randomized, open-label long-term follow-up study (> 5 years) that infliximab administrated within 4 weeks of surgery (5 mg/kg infusions at 0, 2, 6, and every 8 weeks) for 1 year is effective in preventing Crohn's disease relapse.

A recently published study, the first direct prospective comparison between two anti-TNFα in prevention of POR showed that both drugs seem to be effective with no significant difference found between the ADA or IFX group regarding clinical and endoscopic recurrence. At the end of the follow-up there was no significant difference in clinical recurrence between adalimumab and infliximab (1 patient from the two groups developed symptoms), with a slight predominance of endoscopic recurrence in the IFX group (2 patients compared with 1 in the ADA group) (19). They stated in this study that surgery is often required in CD patients, but it may be not be curative and considering the high probability of POR, preventative therapy may be recommended, especially in a group of patients who present risk factors considered in their study such as active smoking, penetrating disease and previous surgery (19).

The only study dedicated to prevention and therapy of POR was performed by Papamichael et al. Their aim was to assess the short and long term efficiency of ADA in preventing and treating postoperative recurrence in CD patients (21). 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. After 2 years of ADA therapy, 6 of 8 patients maintained complete (n = 3) or near complete (n = 3) mucosal healing and 7 of 8 patients remained in clinical remission (21). Our data showed that at 2 years the rate of clinical remission in this sub-group of patients is slightly lower, approximately 75%.

Our data are important because until now it is the only study that compares two biologic agents used to treat post-operative recurrence of Crohn's disease. The strength of this cohort is that it is population-based, because it encompassed all Crohn's patients treated with biologics in Romania (approx. 21 million inhabitants). An important limitation of this study, inherent to a retrospective study is non-uniformity in assessment of some outcome parameters. Giving the fact that the risk of postoperative recurrence increases over time, for a better evaluation of the preventive treatment for POR, a long term prospective open trial is recommended, such as the study conducted by Yoshida et al. (22) showing the effectiveness of infliximab as a preventive therapy for POR in CD.

In conclusion, infliximab and adalimumab are equally efficient in resected patients with CD with a complete response of 68%, a rate of re-resection of 11.7% and a rate of endoscopic recurrence of 35% (overall). Even in non-resected patients the risk of surgical interventions on biological therapy is about 6%. Based on statistical analysis of the results, there are no predictive factors for POR in patients treated with IFX, but those treated with ADA who suffered a post-operative recurrence during therapy were all located in the ileocolonic area (L3), but we failed to prove its significance because of the small sample size.

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