Journal of Crohn's and Colitis (2012) 6, 681–686

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Cyclosporine or infliximab as rescue therapy in severe refractory ulcerative colitis: Early and long-term data from a retrospective observational study

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Received 26 July 2011; received in revised form 25 November 2011; accepted 26 November 2011

KEYWORDS
Ulcerative colitis;
Steroid-refractory;
Cyclosporine;
Infliximab;
Colectomy

Abstract

Introduction: About 30-40% of patients with acute severe ulcerative colitis (UC) fail to respond to intensive intravenous (iv) corticosteroid treatment. Iv cyclosporine and infliximab are an effective rescue therapy in steroid-refractory UC patients but up to now it is still unclear which is the best therapeutic choice.
Methods: We reviewed our series of severe steroid-refractory colitis admitted consecutively since 1994 comparing two historical cohort treated with iv cyclosporine (2 mg/kg) or iv infliximab (5 mg/kg). The main outcome was the colectomy rate at 3 months, 12 months and at the end of the follow-up.
Results: A total of 65 patients were included: 35 in the cyclosporine group and 30 in the infliximab one. At 3 months the colectomy rate was 28.5% in the cyclosporine group and 17% in the infliximab group ($p=0.25$), while 48% versus 17% at 12 months ($p=0.007$, OR 4.7; 95% CI: 1.47-15.16). The 1-2-3 year cumulative colectomy rates were 48%, 54%, 57% in the cyclosporine group, and 17%, 23%, 27% in the infliximab group. At the end of the follow-up the colectomy rate was 60% versus 30% ($p=0.04$, HR 2.2; 95% CI: 1.11-4.86). High level of C reactive protein ($p=0.04$), extensive disease ($p=0.01$) and no azathioprine treatment ($p<0.001$) were related to the risk of colectomy.

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1873-9946/$ - see front matter
doi:10.1016/j.crohns.2011.11.021

Conclusion: This study, despite being retrospective, indicates that both cyclosporine and infliximab are effective in avoiding a colectomy in steroid-refractory UC patients. During the follow-up the risk of a colectomy is higher in patients treated with cyclosporine than with infliximab.

1. Introduction

Acute severe ulcerative colitis (UC) is a dangerous clinical condition, potentially lethal, that requires intensive medical treatment and can lead to a prompt colectomy in case of treatment failure.[1,2] A recent study from Oxford[3] showed that acute colitis, defined by the Truelove and Witt's criteria,[4] affects up to 25% of all patients with UC. Thirty-nine percent of patients with one or more episodes of severe flare underwent colectomy compared to 3.4% of those patients who never needed admission ($p<0.0001$). The introduction of intravenous (iv) corticosteroids has modified the natural history of severe acute relapse[5] but about 30–40% of patients fail to respond to intensive treatment. IV cyclosporine (CsA), a fungal calcineurin inhibitor, at the dosage of 4 mg/kg daily[6], was the first rescue therapy, achieving a short-term improvement in steroid-refractory UC patients (76–85%) although dosage of 2 mg/kg daily resulted equally effective.[1,7,8,9] In the last ten years infliximab (IFX),[10,11,12] which is a monoclonal antibody that binds a free and membrane bound tumor necrosis factor-α, has shown to be an effective treatment for severe attacks of UC, at the dosage of 5 mg/kg, avoiding the risk of colectomy. We reviewed our series of severe steroid-refractory colitis admitted consecutively in our referral center from 1994 up to today comparing two historical cohort of patients treated with CsA or IFX.

2. Methods

2.1. Patients characteristics and drug administration

This retrospective study included two historical cohorts of UC patients with severe relapse refractory to iv steroid treatment administered according to the "Oxford regimen".[5] IV steroid resistant UC is defined as a lack of response to an adequate dosage of steroids within 5–7 days. Criteria for severity were those adopted by both a modified Truelove and Witts and Lichtiger score.[4,6,13] Severity was also assessed by rectal endoscopy and on clinical grounds. At admittance all patients were evaluated with abdominal x-ray, full blood count, blood chemistry and arterial blood gas analysis, in order to exclude toxic megacolon. Since 1997 human cytomegalovirus detection in rectal biopsies and peripheral blood has also been researched, in order to exclude cytomegalovirus infection (in the presence of a positive test we treated the patient with antiviral therapy before the standard treatment). At admittance we alerted the patients and the surgeons about the risk of colectomy.

From 1994 to 2003 all severe patients refractory to iv steroid were treated with iv CsA at the dosage of 2 mg/kg daily adjusting the dosage on the base of the CsA blood levels (therapeutic range 200–250 μg/L). From January 2004 up to today patients with these clinical severe conditions have been treated with iv IFX at the dosage of 5 mg/kg after the conventional screening for infection or malignant diseases. All patients signed a written informed consent before starting both treatments. Patients who responded to iv CsA were switched after 14 days to oral formulation (5 mg/kg daily) for a maximum of 3 months. Patients who responded to IFX, and without clinical signs of intolerance, completed the induction phase with infusions at week 2 and 6 followed by scheduled infusions (5 mg/kg every 8 weeks). In our policy we do not use combo therapy due to the risk of possible severe infections. Three patients received combo therapy only during the induction phase of IFX treatment. The steroid discontinuation was conducted within a 1–1.5 month period by reducing the dose by 25% of the initial dose every ten days.

In patients treated with IFX, azathioprine at the dosage of 2.5 mg/kg daily was started soon after the last infusion. In the CsA group, azathioprine was started together with CsA oral formulation. If previous intolerance or failure of immunosuppressants had been reported, maintenance treatment with azathioprine was excluded.

In all patients in whom CsA or IFX failed, a total colectomy was performed. CsA or IFX failure was defined by the physician after a global assessment and the decision about a continued medical treatment or an emergency colectomy were made on clinical grounds within 5–7 days. Three patients who refused a total colectomy received both treatments: 1 was treated with IFX soon after CsA failure and 2 were treated with CsA soon after IFX failure.

In the case of a new severe UC flare-up (according to the modified Truelove and Witts and Lichtiger score): if this occurred under CsA or IFX treatment a total colectomy was performed. On the contrary a new course of CsA or IFX (according to the drug that had previously allowed the remission) was started and a colectomy was performed in the case of treatment failure.

2.2. Outcomes

The main outcome was the colectomy rate after CsA or IFX rescue therapy failure at 3 months, 12 months and at the end of the follow-up. The secondary outcome was the number of UC relapses which required hospitalization. All responder patients were followed up in our outpatient clinic in order to monitor their clinical conditions, UC relapse requiring hospitalization or not, needing colectomy or any adverse events. Visits were closer in the first month from discharge and then at 2 monthly intervals. At each visit general well-being, physical examination and blood analysis were obtained and recorded in an electronic file. All patients had a minimum follow-up of 12 months.

2.3. Statistical analysis

Data were analyzed using the software package SPSS 15 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as mean (±standard deviation [SD]) or median (range) according to their distribution. Categorical variables were summarized as frequency and percentage. Significant differences were calculated using a χ^2 test for categorical variables and with logistic regression for continuous variables. Demographic and disease variables were related to the main and the secondary outcomes using the logistic regression model at 3 and 12 months and the Mantel Cox model at the end of the follow-up. We considered the following variables: sex, age, smoking habit, family history, disease duration, and disease extension. Differences were considered significant for p-value less than 0.05. Time to colectomy was illustrated with a Kaplan–Meier plot, and differences between groups were tested with a log-rank test.

3. Results

A total of 65 patients were included in the final analysis: 35 in the CsA group and 30 in the IFX one. The patients' characteristics in the two groups were comparable as reported in Table 1. The mean follow-up was 74.7±60.8 months in the CsA group and 33.6±15.5 months in the IFX group. After 3 months from the acute episode, which required CsA or IFX treatment, the colectomy rate was: 28.5% (10/35) in the CsA group and 17% (5/30) in the IFX group (p=0.25). Of these patients 5 and 3, in the CsA and the IFX group respectively, underwent a colectomy between days 8 and 15, while the remaining 5 and 2 respectively underwent a colectomy between days 15 and 30. At 12 months the rate of colectomy increased to 48% in the CsA group versus 17% in the IFX group (p=0.01, OR 4.7; 95% CI: 1.47–15.16).

Table 1 Baseline characteristics of study population.

	Cyclosporine group	Infliximab group	p-value
Number of patients with a Lichtiger's score>10	35	30	–
Male/female	15 (42.8%)/ 20 (57.2%)	15 (50%)/ 15 (50%)	0.56
Mean age±sd (years)	34.9±13.7	37±16.6	0.69
Disease duration (median [range])	36 (1–588)	48 (4–348)	0.65
Smoking habit			0.32
•Non-smokers	28 (80%)	27 (90%)	
•Current smokers	7 (20%)	3 (10%)	
Disease extension			0.13
•Left-side	6 (17%)	10 (33.3%)	
•Extensive colitis	29 (83%)	20 (66.7%)	
Mean hemoglobin value at baseline±sd (g/dl)	9.2±0.7	9.4±0.5	0.45
History of azathioprine/ 6-mercaptourine	15 (42%)	9 (30%)	0.11

In the CsA group all 25 responder patients after the rescue therapy were switched to oral formulation: 13 (52%) of these started azathioprine after oral CsA discontinuation while the remaining 12 (48%) were not able to start azathioprine due to previous intolerance. At the end of the follow-up 11 of the 25 initially responder patients (44%) experienced a severe flare-up of UC and underwent total colectomy: 2 in the group of patients who received azathioprine and 9 in the group of patients who were not able to start azathioprine due to a previous intolerance.

In the IFX group (25 responder patients): 15 patients (60%) continued the treatment every 8 weeks (for 1 year) but only 9 of them were switched to azathioprine (the remaining 6 patients were previously intolerant or non-responder to azathioprine); 5 patients (20%) experienced an adverse event during the induction phase and discontinued IFX, but none of them underwent a colectomy during the follow-up (only 2 of them were maintained with azathioprine while the other 3, intolerant to azathioprine, were maintained with mesalamine); 3 patients (12%) received an initial combo therapy and were then maintained with azathioprine; 1 patient (4%) discontinued IFX because of human cytomegalovirus detection in peripheral blood and because of his age (75 years old), he continued to receive mesalamine as a maintenance treatment; 1 patient (4%) experienced a skin reaction after the induction phase (she was previously intolerant to azathioprine but until now she had avoided colectomy, she continued to receive mesalamine as a maintenance treatment). To summarize, 14 out of 25 patients (56%) started azathioprine in the IFX group.

Four out the 25 initial responder patients (16%) experienced a severe flare-up of UC and underwent a total colectomy: 2 patients were being treated with IFX (they were previously intolerant to azathioprine); 2 patients were being treated with azathioprine, started after IFX discontinuation (1 patient previously experienced lung interstitiopathy during IFX treatment).

The patient who switched to IFX after CsA failure avoided colectomy at the end of the follow-up. Regarding the 2 patients treated with CsA after IFX failure both underwent colectomy.

The 1–2–3 year cumulative colectomy rates were 48%, 54%, and 57% in the CsA group, and 17%, 23%, and 27% in the IFX group, as shown by the Kaplan–Meier plot in Fig. 1. At the end of the follow-up the colectomy rate was: 60% (21/35) in the CsA group and 30% (9/30) in the IFX group (p=0.04, HR 2.2; 95% CI: 1.11–4.86). No difference was observed regarding the risk of re-hospitalization at 12 months (p=0.34, OR 0.2; 95% CI 0.532–5.805) and during the follow-up (p=0.72, HR 1.13; 95% CI: 0.48–2.63).

Considering the overall population, high level of C reactive protein (p=0.04, OR 2.9; 95% CI: 1.18–8.28), extensive disease (p=0.01, OR 5.5; 95% CI: 1.57–19.01), and no azathioprine treatment after the rescue therapy (p<0.01, OR 8.7; 95% CI: 2.49–30.12) were related to the risk of colectomy. No differences in terms of side effects were observed between the two groups and no serious adverse events were recorded. No serious post-operative complications were recorded in both groups. One patient treated with CsA developed a mild side effect (cholestatic hepatitis) without discontinuing the drug (questionable relationship with CsA) while 6 patients in the IFX group discontinued the treatment

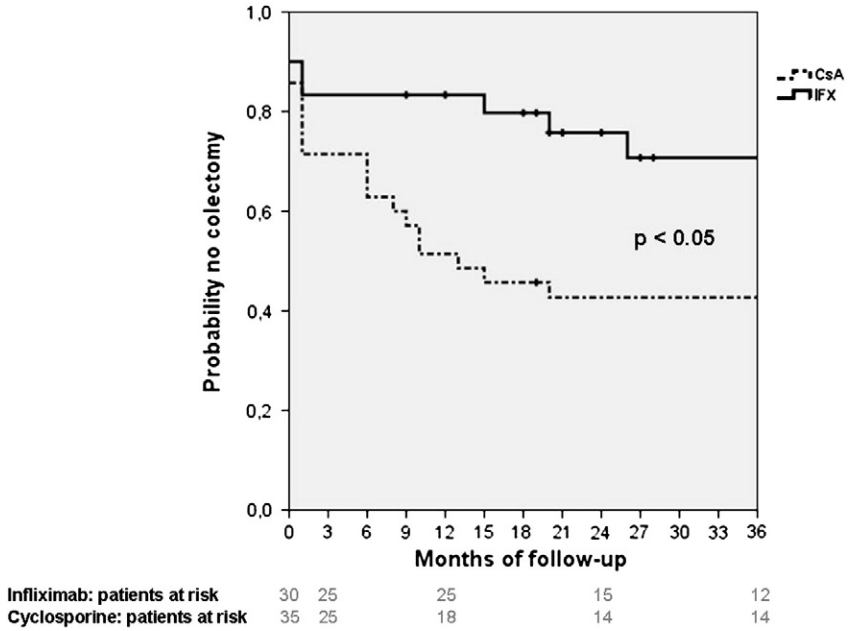

Figure 1 Kaplan–Meier plot showing probability of colectomy-free survival in relation to time after rescue therapy with cyclosporine or infliximab.

due to an acute drug reaction (5 during the induction phase and 1 during the maintenance treatment). No mild or severe drug-related adverse events were observed in the 3 patients who received both treatments.

4. Discussion

This retrospective study shows that CsA and IFX are equally effective as a rescue therapy in severe steroid-refractory UC at 3 months, while IFX seems more effective in avoiding colectomy during the follow-up. Up to now current national and international guidelines suggest both treatments as a rescue therapy.[14,15] Preliminary results of a randomized controlled trial, which has compared CsA with IFX in iv steroid-resistant UC as a salvage therapy (CYSIF trial), were presented at the European Crohn's and Colitis Organization 2011 and Digestive Disease Week 2011 meetings.[16,17] One hundred and sixteen patients with steroid-refractory acute severe UC were recruited to receive either 2 mg/kg daily iv CsA, followed by oral formulation (4 mg/kg daily) for 3 months or IFX (5 mg/kg) at weeks 0, 2 and 6. Clinical response at day 7 and steroid-free remission at day 98 were comparable between the groups (about 60%) with no differences in terms of colectomy and adverse event rates. The early response (7 days) to either therapy exceeded 80%. On the contrary, recently Sjöberg et al. underwent a retrospective observational study[18] comparing two cohorts: a Swedish-Danish cohort of 49 patients treated with a single infusion of IFX and an Austrian cohort of 43 patients treated with iv CsA. This study showed a colectomy-free survival rate at 3 months of 67% in the IFX cohort versus 93% in the CsA cohort ($p=0.002$). At 12 months the colectomy-free survival rate was 57% versus 77% ($p=0.03$). Cox regression analysis showed a hazard ratio for the risk of colectomy in IFX-treated patients of 11.2 at 3 months and of 3.0 at 12 months in comparison with CsA-treated patients. The authors concluded that the colectomy risk was significantly lower after rescue therapy with CsA than with a single infusion of IFX.

Another retrospective study, performed by the Royal Brisbane group[19] (in abstract only at present), compared IFX and CsA as salvage therapy in acute severe UC reporting similar findings. This study analyzed 72 patients comparing the colectomy rates as a rescue therapy and at 12 months. After salvage therapy 52% (23/44) in the CsA group and 18% (5/28) in the IFX group ($p=0.003$) proceeded to a total colectomy before discharge, while at 12 months the colectomy rate was 68% and 44% for CsA and IFX respectively ($p=0.04$). In our study, according to the CYSIF trial, we did not observe a significant difference at 3 months between the 2 cohorts of patients, treated respectively with CsA and IFX. Nevertheless at 12 months the rate of colectomy increased to 48% in the CsA group versus 17% in the IFX group ($p=0.01$). Therefore at 3 years more patients in the CsA group were operated on than in the IFX group.

Our long-term data (colectomy rate of 60% in the CsA group), also, are in agreement with the observation data from Leuven, which showed that 88% of patients with CsA-induced remission underwent colectomy at the end of the follow-up (7 years).[20]

In IFX treated patients our results differ from those reported by the Swedish trial at 3 and 36 months[12,13] where the colectomy rate in the IFX group was respectively 29% and 50% so higher than ours. These differences can be explained by the dose of IFX: in our study 56% of responder patients maintained administration every 8 weeks while in Järnerot's study a single IFX infusion was adopted and only 17.6% (3/17) of these received scheduled treatment, as reported in the 3-year follow-up study. It is well known that the number of IFX infusions affects the final outcome with early higher colectomy rates in those receiving a single infusion, compared with those receiving two or more

infusions (p=0.001).[21] Data from the same Italian population, published only as an abstract, showed that a three-dose induction regimen with IFX had a 90-day and 12-month colectomy rate of 17% and 22% respectively.[22]

Some authors evaluated the possible factors affecting the efficacy of CsA or IFX as a rescue therapy in steroid-refractory UC, showing how azathioprine after CsA treatment significantly reduced the colectomy rate (66.7% vs 30.5%, p=0.041)[23] while, in IFX treated patients, the trough serum concentration of IFX may be closely related to the final outcome. An undetectable trough level was a strongest predictor of colectomy (OR 9.3; 95% CI 2.9–29.9; p<0.001).[24] In the present study 52% and 56% of patients started azathioprine after CsA or IFX respectively with a low colectomy rate during the follow-up (p<0.01); we cannot exclude that the increased risk of colectomy in patients not receiving azathioprine as maintenance treatment could be related to previous failure of azathioprine. Trough serum concentration of IFX was not performed.

Three of our patients refused colectomy despite failure of the rescue therapy with CsA or IFX and in 1 of these patients colectomy was avoided. Up to now there is no strong evidence of the efficacy of sequential therapy, with either CsA or IFX after failing to respond to the other. Results from a cohort of patients from the Mount Sinai Hospital in New York suggested that patients receiving IFX followed by CSA or vice versa have an increased risk of serious adverse events and mortality[25] but some other evidence suggests that the successive use of both agents is an effective therapeutic option.[26,27] Nevertheless renowned and expert authors suggest that clinicians should carefully consider if the number of colectomies avoided by the consecutive use of CsA and IFX outweighs the cumulative opportunistic infection risk.[1,9]

The limits of this study are the retrospective nature and the comparison between two cohorts (historical) enrolled in different periods of time. The data obtained from this study are quite reliable considering the fact that the characteristics of the two groups were comparable, that the main outcome chosen (surgery) in this study was not biased by subjective evaluation, and that the clinical management of severe colitis has not changed within the last two decades.

In conclusion, despite the limits above quoted, our data indicates that both CsA and IFX are effective in avoiding a colectomy after a severe UC flare-up refractory to iv steroids. Nevertheless during the follow-up the risk of colectomy is higher in patients with extensive colitis or treated with CsA instead of IFX. Both the drugs were equally safe without severe adverse events. The incoming results from the CYSIF trial will strengthen the current evidence in this setting of patients making the best choice of medical salvage therapy clearer.

Conflict of interest

There is no conflict of interest.

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