

Seymour Katz, M.D., Series Editor

Infliximab for Refractory Ulcerative Proctitis



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INTRODUCTION

In population-based studies, ulcerative colitis was confined to the rectum at the time of diagnosis in 22% to 59% of patients.¹⁻⁶ The 2-yr, 5-yr and 10-yr cumulative rate of relapse after the first diagnosis was respectively of 42%, 57% and 84% for all patients with ulcerative proctitis (UP) at diagnosis.⁷⁻⁹ UP may result in distressing symptoms, including stool frequency, tenesmus, urgency and bleeding.^{8,10} Despite the significant benefits of rectally administered aminosalicylates and corticosteroids,^{10,11} some patients with UP and good observance fail to improve and require additional medical therapy.

The management of UP refractory to standard medications remains a challenge in clinical practice, as few data are evidence-based.¹⁰ Several medications have been tested to treat refractory UP. In randomized controlled trials, antibiotics,¹²⁻¹⁵ cyclosporine en-

mas¹⁶ and oral methotrexate¹⁷ were not significantly effective to induce and maintain long-term clinical response and remission. Azathioprine^{18,19} and tacrolimus²⁰ were more effective than 5-aminosalicylate/mycophenolate mofetil and placebo, respectively, to induce short-term clinical response in refractory ulcerative colitis, but were associated with a higher incidence of adverse events. Intramuscular methotrexate²¹ and rectal tacrolimus ointment^{22,23} have been assessed in small open labeled studies, with encouraging results that need to be confirmed in large prospective studies. There is a lack of sufficient data or fair results for alternative and miscellaneous treatment including nicotine, heparin, short-chain fatty acid or probiotics.²⁴⁻²⁷ Although an invasive procedure, appendectomy has recently shown promising results.²⁸ Overall, these results remain difficult to interpret due to small sample size and the lack of well-designed published studies supporting their efficacy for refractory UP.

Infliximab (Remicade; Centocor, Malvern, PA), a tumor necrosis factor antagonist, has changed the way

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of treating inflammatory bowel diseases refractory to standard medications. Two large placebo-controlled, randomized trials, namely ACT 1 and ACT 2, demonstrated that infliximab is effective to induce and maintain clinical response in ulcerative colitis.²⁹ However, patients with UP were excluded from both studies. In a retrospective study of 121 patients treated for ulcerative colitis with infliximab, only 3 patients had UP but were not specifically studied.³⁰ In a prospective pilot study evaluating the efficacy of local tacrolimus for UP, tacrolimus was prescribed for infliximab failure in 4 out of 8 patients.²³ Recently, topical administration of infliximab was found to be effective in one patient with chronic refractory proctitis.³¹

Importantly, patients with UP showing an aggressive disease course, with frequently relapsing proctitis and refractory disease to conventional treatment, are more prone to show proximal extension at a later date,⁷⁻⁹ and are colectomized to a higher extent.^{2,8} Because some data suggest that early aggressive treatment of UP may prevent or delay proximal extension, there is an urgent need to better evaluate the efficacy of potent therapies such as infliximab in treating these patients.³²

We evaluated for the first time the long-term outcome of refractory UP treated with infliximab therapy in a retrospective multicenter study.

METHODS

Study Population

All hospital records of adult patients treated with infliximab for refractory ulcerative colitis at 6 tertiary referral centers in France between January 2005 and September 2009 were reviewed. Proctitis was defined according to the Montreal classification.³³

Short-term and long-term clinical responses were evaluated as previously described.^{30,34,35} The “short-term response” was defined as the result of induction therapy with infliximab and “long-term response” was defined as clinical efficacy at the maximal follow-up. Both short- and long-term clinical responses were defined as complete in the absence of diarrhea and blood and if a steroid-sparing effect was noted, and partial if there was marked clinical improvement but

still persistent rectal blood loss.^{30,36} To assess rectal disorders, we also recorded the presence of stool urgency, incontinence, tenesmus and rectal pain at first infliximab infusion and during the follow-up. Rectal disorders were considered as “present” if one of these items was reported, while rectal disorders were defined as “absent” if none was recorded.

To assess endoscopic activity of proctitis, three levels of activity were defined: (1) normal, (2) mild with erythema, friability erosion and lack of spontaneous bleeding, and (3) severe with ulceration and spontaneous bleeding.²⁹

RESULTS

The baseline characteristics of the 13 patients at first infliximab infusion are indicated in Table 1.

Concomitant medications at infliximab therapy initiation are summarized in Table 2.

Short-term Clinical and Biological Efficacy (Table 2)

Two out of 13 patients (15%) were judged as primary non-responders. A total of 11 out of 13 (85%) patients experienced clinical improvement after treatment with infliximab: complete clinical response was observed for 9 out of the 11 patients (82%) and a partial response for two subjects (18%). All subjects (n = 8) with concomitant immunosuppressant had a clinical response, which was judged as complete in 6 out of the 8 patients. Rectal disorders were improved in 9 out of the 11 primary responders (82%).

Following infliximab induction therapy, the mean C-reactive protein (CRP) level fell from 12.8 mg (S.D. = 15.1; range, 1–55) to 4.7 mg (S.D. = 4.1; range 0.6–12; data available at baseline and after induction therapy in 10 of 13 patients).

Long-term Outcome: Clinical, Biological and Endoscopic Responses

After a median follow-up of 17 months (SD 13 months; range 3–48), the evaluation of clinical activity at last follow-up revealed a partial (n = 2) or complete (n = 7) clinical response in 9 of the 11 primary respon-

Table 1.
Baseline characteristics of 13 patients with refractory ulcerative proctitis.

Patient No.	Sex	Age (yr)	Disease duration (months)	Previous surgery	Previous treatment		Number of bowel movements/24 hours	Presence of bloody stools*	Rectal disorders	Endoscopic activity
					Enema, ointment, suppository	Systemic medications				
1	M	61	267	NO	ASA	ASA,CS, IS, Cyclo	6	Severe	Present	Severe
2	M	46	131	NO	ASA	ASA,CS, IS	4	None	Present	Normal
3	M	65	45	NO	ASA, CS	ASA,CS, IS	6	Mild	Present	Mild
4	M	31	24	NO	ASA	ASA,CS, IS	10	Severe	Present	Severe
5	M	55	195	NO	ASA, CS	ASA,CS, IS	15	Severe	Present	Severe
6	M	54	75	NO	ASA	ASA,CS, IS	15	Severe	Present	Severe
7	M	42	12	NO	ASA	ASA,CS	10	Mild	Present	Mild
8	M	28	12	NO	ASA, CS	ASA,CS, IS, Cyclo	3	Mild	Present	Mild
9	M	37	3	NO	ASA, CS	CS, IS	2	None	Present	Mild
10	M	26	44	NO	ASA, CS	ASA,CS	20	Mild	Present	Mild
11	M	54	7	Sigmoid-ectomy	ASA, CS	ASA, CS, IS	8	Severe	Present	Severe
12	F	55	4	NO	ASA, CS	ASA,CS, IS	8	Severe	Present	Severe
13	M	42	29	NO	ASA, CS	ASA,CS, IS	6	Severe	Present	Mild

M, Male; F, female; yr, years ; IFX, infliximab; ASA, aminosaliclylate; IS, immunosuppressant (azathioprine, 6 mercaptopurine, methotrexate); CS, corticosteroid; Cyclo, cyclosporine

*As judged by their physician.

ders (82%). Of note, rectal disorders disappeared in all 9 patients.

The 4 remaining patients had symptomatic disease at last follow-up, including the 2 patients who were considered as primary non-responders. Both of these patients (Patients 5 and 10) were being treated with oral corticosteroid at last follow-up. Two patients (Patients 2 and 8) who were considered as primary responders lost response to infliximab over time and were secondary non-responders: one patient treated with scheduled infliximab therapy without concomitant immunosuppressant had a disease extension to left-sided colitis after discontinuation of corticosteroid therapy and finally underwent proctocolectomy (Patient 2). The other one (Patient 8) had complete short-term clinical response with disappearance of diarrhea and blood in stools, but had a persistent rectal disorder at last follow-up. This patient had an early relapse after infliximab induction therapy and did not experience any clinical improvement despite inflix-

imab optimization by dose escalation at the fourth infusion. Treatment was changed to oral tacrolimus and methotrexate without any response on clinical disease activity or rectal disorder.

At last follow-up, the CRP level was available for 7 patients. When including all 7 subjects in the analysis, the mean CRP level was 14.4 mg/L (S.D. = 22.2; range 0.5–59). Excluding primary non-responders did not influence this result, with a mean CRP level of 14.1 mg/L (S.D. = 25.2; range 0.5–59). When excluding both primary and secondary non-responders, the mean CRP level was only 2.9 mg/L (S.D. = 2; range 0.5-5).

All patients had endoscopic evaluation at baseline. During follow-up, 7 patients also had endoscopic evaluation of the rectum after infliximab initiation. This showed an improvement in mucosal lesions in 4 patients (complete mucosal healing in 2 patients and mild endoscopic activity in 2 patients), stable endoscopic lesions with persistent mild endoscopic disease in two patients, and persistent severe rectal disease in

Table 2.
Short-term and long-term responses to infliximab in the 13 patients with refractory ulcerative proctitis.

Patient No.	Number of IFX infusions	Short-term response			Follow-up (months)	Maintenance treatment (IFX)	Long-term response		Endoscopy at last news	Treatment at last news
		Concomitant medications	Clinical response	Rectal disorders			Clinical response	Rectal disorders		
1	17	ASA, IS	Complete	Absent	28	YES	Complete	Absent	Mild	IFX
2	4	ASA, CS	Complete	Present	21	YES	Absent	—	—	Procto-colectomy
3	4	None	Complete	Absent	5	YES	Complete	Absent	—	IFX
4	18	CS, IS	Complete	Absent	28	YES	Complete	Absent	Complete mucosal healing	IFX
5	3	CS	Absent	Present	29	Primary non responder	Absent	Present	Mild	CS
6	6	CS, IS	Partial	Absent	12	YES	Complete	Absent	—	IFX
7	4	ASA	Complete	Absent	3	YES	Complete	Absent	—	IFX
8	4	IS	Complete	Present	9	YES	Absent	Present	Mild	Tacrolimus IS
9	28	CS, IS	Complete	Absent	48	YES	Complete	Absent	Mild	IFX, IS
10	3	None	Absent	Present	6	Primary non responder	Absent	Present	—	CS
11	3	ASA, IS	Partial	Absent	6	NO	Partial	Absent	—	IFX
12	3	CS, IS	Complete	Absent	18	NO	Partial	Absent	Severe	ADA*, CS, IS
13	9	ASA, IS	Complete	Absent	12	YES	Complete	Absent	Complete mucosal healing	IFX

IFX, infliximab; ASA, aminosalicylate; IS, immunosuppressant (azathioprine, 6 mercaptopurine, methotrexate); ADA, adalimumab
*Switch from infliximab to adalimumab due to patient preference.

one patient, as defined above. Interestingly, endoscopic response was generally associated with clinical response: There was a discrepancy between endoscopic and clinical response in only two patients: patients 5 and 8, who respectively had severe or mild endoscopic lesions at baseline, were primary and secondary non-responders at last follow-up despite mild endoscopic activity after infliximab therapy initiation.

Adverse Events

Infliximab infusions were generally well tolerated. None of the 13 patients had any acute infusion reac-

tion. Only two patients experienced adverse events. One developed psoriasiform lesions leading to infliximab discontinuation. The other developed several infections, with left-sided diverticulitis and bursitis of the knee. He was treated with concomitant immunosuppressant and oral steroid therapy. Both infections had a favorable outcome after administration of broad-spectrum antibiotics, so infliximab therapy could be continued. No opportunistic, tuberculosis infections, malignancies or lymphoma were observed throughout the follow-up period.

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DISCUSSION

This study shows for the first time that infliximab treatment may be effective for both induction and maintenance of clinical response in refractory UP.

Following infliximab induction therapy, 11 out of 13 (85%) patients experienced clinical improvement after treatment with infliximab, with 9 of the 11 (82%) also experiencing improvement in rectal disorders. Long-term outcome showed a complete clinical response for half of the patients with refractory UP. These results are in line with previous reports showing a clinical response in patients with pancolitis or left-sided colitis treated with infliximab at short term in about 63–69.4% of patients and at long term in 38.8–43% of patients.^{29,30} Of note, 9 of the 11 primary responders maintained a complete response at maximal follow-up, as judged by disease activity and the absence of rectal disorders. This finding is also consistent with that obtained in a large monocenter retrospective study evaluating infliximab in left-sided and pancolitis, and showing that 68% of patients with initial response to infliximab had sustained clinical response during follow-up.³⁰

Interestingly, clinical response was accompanied by a decrease in CRP levels and an improvement in endoscopic lesions of the rectum. The drop in CRP levels is a known factor associated with clinical response in ulcerative colitis.³⁰ Mucosal lesions were improved in 4 of the 7 patients with endoscopic assessment after infliximab initiation, thus confirming the efficacy of infliximab therapy in this indication.

In our series, only one patient relapsed after infliximab induction: he progressed to pancolitis and finally underwent proctocolectomy. Of note, the safety profile of infliximab was consistent with previous experience with this drug in UC.^{29,30,34} Overall, these results indicate that infliximab may be effective in treating refractory UP.

The main limitation is the lack of control arm. However, the rates of response to placebo in patients with severe and resistant ulcerative colitis in randomized control trials are low, ranging from 10 to 33% at short term and from 6.6 to 14% in the long term.^{20,29} In addition, only patients who had active disease despite treatment with conventional therapy, including local aminosalicylate and corticosteroid therapy, were included in the study.

Importantly, the median follow-up was 17 months. A long-term follow-up is required to assess the sustained efficacy of medical treatment in refractory UP, which is known to relapse frequently, and because refractory disease is more prone to having a complicated outcome.^{8,9,14} Furthermore, this was a multicenter study. Infliximab therapy is rarely used to treat UP in clinical practice. By screening a total of 420 patients treated with anti-TNF therapy for ulcerative colitis at 6 referral centers in France, we were able to identify and analyze the data of 13 patients. Finally, because of the retrospective study design and the inherent bias in interpreting clinical response on medical records, we decided to assess clinical response not only by using the judgment of the treating physician but also by recording the presence or not of objective Mayo criteria such as diarrhea and blood in the stools.^{30,36} In addition, the absence of rectal disorders was defined as the absence of all predefined items, namely stool urgency, incontinence, tenesmus and rectal pain.

Collectively, our findings indicate that infliximab may be effective and safe in inducing and maintaining a clinical response in patients with refractory UP. ■

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