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INFLIXIMAB FOR REFRACTORY ULCERATIVE PROCTITIS

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For Peer Review

SUMMARY

Background: Efficacy of infliximab in treating ulcerative proctitis is unknown.

Aim: To evaluate clinical, biological and endoscopic efficacy of infliximab therapy in refractory proctitis.

Methods: The charts of 420 patients treated with infliximab for ulcerative colitis were reviewed. Thirteen patients were treated with infliximab for refractory ulcerative proctitis in six referral centers between 2005 and 2009.

Results: Following infliximab therapy induction, 9/13 patients (69%) had a complete response (defined as absence of diarrhea and blood), 2/13 (15%) had a partial response and 2/13 (15%) were primary non-responders. The median follow-up was 17 months (range, 3-48). Among the 11 patients with clinical response after infliximab induction therapy, 9 (82%) patients maintained response at last news. Disappearance of rectal disorders was observed in all 9 patients who maintained clinical response at last news. Following infliximab induction therapy, the mean CRP level fell from 12.8 mg/L to 4.7 mg/L. Endoscopic evaluation was performed before and after infliximab in 7 patients, showing an improvement in mucosal lesions in 4 patients, persistent mild endoscopic activity in 2 patients, and no improvement in one patient. One patient underwent proctocolectomy.

Conclusion: Infliximab therapy **seems** to be effective in inducing and maintaining clinical response in refractory ulcerative proctitis.

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 enemas¹⁶ 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 of treating inflammatory bowel diseases refractory to standard medications. Two large placebo-controlled, randomized trials, namely ACT 1 and ACT 2, demonstrated

1
2
3 that infliximab is effective to induce and maintain clinical response in ulcerative colitis.²⁹
4
5
6 However, patients with UP were excluded from both studies. In a retrospective study of 121
7
8 patients treated for ulcerative colitis with infliximab, only 3 patients had UP but were not
9
10 specifically studied.³⁰ In a prospective pilot study evaluating the efficacy of local tacrolimus
11
12 for UP, tacrolimus was prescribed for infliximab failure in 4 out of 8 patients.²³ Recently,
13
14 topical administration of infliximab was found to be effective in one patient with chronic
15
16 refractory proctitis.³¹
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18

19
20 Importantly, patients with UP showing an aggressive disease course, with frequently relapsing
21
22 proctitis and refractory disease to conventional treatment, are more prone to show proximal
23
24 extension at a later date,⁷⁻⁹ and are colectomized to a higher extent.^{2, 8} Because some data
25
26 suggest that early aggressive treatment of UP may prevent or delay proximal extension, there
27
28 is an urgent need to better evaluate the efficacy of potent therapies such as infliximab in
29
30 treating these patients.³²
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32

33
34 The aim of this study was therefore to evaluate the long-term outcome of refractory UP
35
36 treated with infliximab therapy in a retrospective multicenter study.
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40 41 **METHODS**

42 43 **Study population**

44
45 All hospital records of adult (age > 18 yr) patients treated with infliximab for ulcerative colitis
46
47 at 6 tertiary referral centers in France (University Hospitals of Rennes, Nancy, Saint-Etienne,
48
49 Nantes, Lyon, and Nice) between January 2005 and September 2009 were reviewed. A
50
51 centralized diagnostic index was first used to identify all patients with diagnosis of ulcerative
52
53 colitis. The database of these patients with ulcerative colitis was then compared to the
54
55 pharmacy records of all patients treated with infliximab at these six hospitals. All adult
56
57 patients with documented proctitis refractory to standard medication at first infliximab
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59
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1
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3 infusion and an established diagnosis of ulcerative colitis based on clinical, radiological,
4
5 endoscopic and/or histological evidence were included. Proctitis was defined according to the
6
7 Montreal classification.³³

8
9
10 Infiximab was administered initially at a dose of 5 mg/kg as a 2-h i.v. infusion. Following
11
12 infiximab induction therapy, which consisted of 3 infusions at weeks 0, 2, and 6, the patients
13
14 received various infiximab regimens, depending on the preferences of each treating
15
16 physician. Maintenance treatment was individually tailored by treating physicians. Scheduled
17
18 maintenance treatment was defined as if infiximab was intentionally planned every 8
19
20 weeks.^{30, 34, 35} All concomitant medications were recorded, and medication was included in the
21
22 analysis only if total drug exposure was superior to 3 months after first infiximab infusion.
23
24

25
26 All adverse events occurring during or after the first infiximab infusion and until last news
27
28 were collected. Acute infusion reactions were defined as any adverse event that occurred
29
30 during or within one hour after the infusion of infiximab.^{30, 34, 35}

31
32
33 All endoscopic and clinical reports mentioning the evolution of UP after first infiximab
34
35 infusion were reviewed.

36
37
38 Short-term and long-term clinical responses were evaluated as previously described.^{30, 34, 35}

39
40 The “short-term response” was defined as the result of induction therapy with infiximab and
41
42 “long-term response” was defined as clinical efficacy at the maximal follow-up. Both short-
43
44 and long-term clinical responses were defined as complete in the absence of diarrhea and
45
46 blood and if a steroid-sparing effect was noted, and partial if there was marked clinical
47
48 improvement but still persistent rectal blood loss.^{30, 36} To assess rectal disorders, we also
49
50 recorded the presence of stool urgency, incontinence, tenesmus and rectal pain at first
51
52 infiximab infusion and during the follow-up. Rectal disorders were considered as “present” if
53
54 one of these items was reported, while rectal disorders were defined as “absent” if none was
55
56 recorded.
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3 To assess endoscopic activity of proctitis, three levels of activity were defined: (1) normal, (2)
4 mild with erythema, friability erosion and lack of spontaneous bleeding, and (3) severe with
5 ulceration and spontaneous bleeding.²⁹
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7
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9

10 11 12 **Statistical analysis**

13
14
15 Owing to small sample size, statistical analysis was limited to descriptive statistics.
16
17 Quantitative variables were described as mean \pm standard deviation (SD) and categorical
18 variables were presented as counts and percent of the cohort.
19
20
21

22 23 24 **RESULTS**

25 26 27 **Baseline characteristics of the patients**

28
29 A total of 420 patients were treated with infliximab for ulcerative colitis at the six referral
30 centers between January 2005 and September 2009. A total of 13 patients were treated with
31 infliximab for refractory UP. The baseline characteristics at first infliximab infusion are
32 indicated in Table 1. The mean age of our population was 47 years (SD=12.7; range, 27-66)
33 and the mean duration of UP was 5.4 years (SD=6.9; range 0.2-22.2). Except for patient 2
34 who had a corticoid-dependent disease, all patients had active UP with diarrhea and/or bloody
35 stools. All patients also had rectal disorders at time of first infliximab infusion.
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46 Only one patient was an active smoker at baseline. One patient had extra-intestinal
47 rheumatologic disease. One patient had prior intestinal surgery that was not related to
48 ulcerative colitis and consisted in a sigmoidectomy for diverticular disease performed 10
49 years before the diagnosis of ulcerative colitis.
50
51
52

53
54
55 Of the 13 patients, 11 (85 %) had been treated with immunosuppressants (thiopurine,
56 methotrexate) before starting infliximab. Two patients had prior exposure to intravenous
57 corticosteroid therapy, and two patients had received cyclosporine before infliximab
58
59
60

1
2
3 initiation. All patients had received prior rectal 5-aminosalicylate and prior oral corticosteroid
4
5 therapy.
6
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10 **Infliximab therapy and concomitant medications**

11
12 Infliximab was prescribed for UP refractory to both rectal 5-aminosalicylate and oral
13
14 corticosteroid therapy in all 13 patients, and UP was also refractory to immunosuppressants in
15
16 11 patients.
17

18
19 All patients received induction therapy with 3 infliximab infusions at weeks 0, 2 and 6. Four
20
21 out of 13 patients (15%) received only infliximab induction therapy, while the 9 remaining
22
23 patients (85%) had scheduled infliximab treatment. In these patients, the mean number of
24
25 infliximab infusions after induction therapy was 7 (S.D. =8.6; range, 1-25).
26
27

28
29 Concomitant medications at infliximab therapy initiation are summarized in Table 2. A total
30
31 of 8 patients were treated with concomitant immunosuppressants and 6 patients had
32
33 concomitant corticosteroid therapy.
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38

39 **Short-term clinical and biological efficacy (Table 2)**

40
41 Short-term efficacy could be assessed for all 13 patients. Two out of 13 patients (15%) were
42
43 judged as primary non-responders. One primary non-responder had no concomitant treatment,
44
45 while the other one was receiving concomitant oral corticosteroid at the time of infliximab
46
47 initiation. A total of 11 out of 13 (85%) patients experienced clinical improvement after
48
49 treatment with infliximab: complete clinical response was observed for 9 out of the 11
50
51 patients (82%) and a partial response for two subjects (18%). All subjects (n=8) with
52
53 concomitant immunosuppressant had a clinical response, which was judged as complete in 6
54
55 out of the 8 patients. Rectal disorders were improved in 9 out of the 11 primary responders
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57
58 (82%).
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3 Following infliximab induction therapy, the mean C-reactive protein (CRP) level fell from
4
5 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
6
7 baseline and after induction therapy in 10 of 13 patients).
8
9

10 11 12 **Long-term outcome: clinical, biological and endoscopic responses**

13
14
15 Information regarding long-term follow-up was available for all patients (n=13). After a
16
17 median follow-up of 17 months (SD 13 months; range 3-48), the evaluation of clinical activity
18
19 at last news revealed a partial (n=2) or complete (n=7) clinical response in 9 of the 11 primary
20
21 responders (82%). Of note, rectal disorders disappeared in all 9 patients.
22
23

24
25 The 4 remaining patients had symptomatic disease at last news, including the 2 patients who
26
27 were considered as primary non-responders. Both of these patients (Patients 5 and 10) were
28
29 being treated with oral corticosteroid at last news. Two patients (Patients 2 and 8) who were
30
31 considered as primary responders lost response to infliximab over time and were secondary
32
33 non-responders: one patient treated with scheduled infliximab therapy without concomitant
34
35 immunosuppressant had a disease extension to **left-sided** colitis after discontinuation of
36
37 corticosteroid therapy and finally underwent proctocolectomy (Patient 2). The other one
38
39 (Patient 8) had complete short-term clinical response with disappearance of diarrhea and
40
41 blood in stools, but as patient 2 had a persistent rectal disorder after infliximab induction
42
43 therapy. This patient had an early relapse after infliximab induction therapy and did not
44
45 experience any clinical improvement despite infliximab optimization by dose escalation at the
46
47 fourth infusion. Treatment was changed to oral tacrolimus and methotrexate without any
48
49 response on clinical disease activity or rectal disorder.
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55 Among the 8 patients who were primary responders and had concomitant immunosuppressant
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57 at baseline, 7 patients had maintained their clinical response without any rectal disorder at last
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59 news.
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3 During follow-up, infliximab optimization was necessary in 3 patients. Two patients (patients
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5 1 and 9) had a complete clinical response at last news, whereas the third one (Patient 8) had
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7 not experienced any improvement in clinical symptoms despite dose escalation and was
8
9 considered a secondary non-responder.
10

11
12 At last news, the CRP level was available for 7 patients. When including all 7 subjects in the
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14 analysis, the mean CRP level was 14.4 mg/L (S.D. = 22.2; range 0.5-59). Excluding primary
15
16 non-responders did not influence this result, with a mean CRP level of 14.1 mg/L (S.D. =25.2;
17
18 range 0.5-59). When excluding both primary and secondary non-responders, the mean CRP
19
20 level was only 2.9 mg/L (S.D. =2; range 0.5-5).
21
22

23
24 All patients had endoscopic evaluation at baseline. During follow-up, 7 patients also had
25
26 endoscopic evaluation of the rectum after infliximab initiation. This showed an improvement
27
28 in mucosal lesions in 4 patients (complete mucosal healing in 2 patients and mild endoscopic
29
30 activity in 2 patients), stable endoscopic lesions with persistent mild endoscopic disease in
31
32 two patients, and persistent severe rectal disease in one patient, as defined above.
33
34 Interestingly, endoscopic response was generally associated with clinical response: the two
35
36 patients with complete mucosal healing at last news who had severe (patient 4) and mild
37
38 (patient 13) lesions at infliximab initiation were in clinical response at last news, whereas
39
40 patient 12 with severe mucosal lesions persisting after infliximab induction therapy was a
41
42 secondary non-responder to infliximab therapy. The 4 remaining patients had mild endoscopic
43
44 activity at last news: patients 1 and 9, who respectively had severe and mild endoscopic
45
46 lesions at time of infliximab initiation, had a complete clinical response at last news. Hence,
47
48 there was a discrepancy between endoscopic and clinical response in only two patients:
49
50 patients 5 and 8, who respectively had severe or mild endoscopic lesions at baseline, were
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52 primary and secondary non-responders at last news despite mild endoscopic activity after
53
54 infliximab therapy initiation.
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Adverse events

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

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.

Two randomized trials, namely ACT 1 and ACT 2, demonstrated the efficacy of infliximab in ulcerative colitis, but UP were excluded from both studies²⁹, whereas the monocenter retrospective study from Leuven did not specifically report the outcome of 3 patients with UP treated with infliximab.³⁰

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,

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3 as judged by disease activity and the absence of rectal disorders. This finding is also
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5 consistent with that obtained in a large monocenter retrospective study evaluating infliximab
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7 in left-sided and pancolitis, and showing that 68% of patients with initial response to
8
9 infliximab had sustained clinical response during follow-up.³⁰ Because infliximab efficacy for
10
11 UP was broadly similar to that reported for left-sided colitis and extensive colitis, our results
12
13 suggest that UP may be included in large international clinical trials evaluating the efficacy of
14
15 anti-TNF agents in ulcerative colitis.
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19
20 Interestingly, clinical response was accompanied by a decrease in CRP levels and an
21
22 improvement in endoscopic lesions of the rectum. The drop in CRP levels is a known factor
23
24 associated with clinical response in ulcerative colitis.³⁰ Mucosal lesions were improved in 4 of
25
26 the 7 patients with endoscopic assessment after infliximab initiation, thus confirming the
27
28 efficacy of infliximab therapy in this indication.
29
30

31
32 Meucci et al. reported that 14% of patients with UP presented one or more features consistent
33
34 with a refractory disease, indicating that, in some patients with UP, the disease course is not
35
36 as mild as generally assumed.⁸ This aggressive course was associated with an increased risk
37
38 of proximal disease extension and finally colectomy.^{2, 8} In our series, only one patient
39
40 relapsed after infliximab induction: he progressed to pancolitis and finally underwent
41
42 proctocolectomy. Of note, the safety profile of infliximab was consistent with previous
43
44 experience with this drug in UC.^{29, 30, 34} Overall, these results indicate that infliximab may be
45
46 effective in treating refractory UP.
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50
51 We were not able to look for predictors of response to infliximab due to small sample size.
52
53 Despite this limitation, patients with concomitant immunosuppressant administration seemed
54
55 to have higher rates of clinical response and a longer duration of response to infliximab.
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57 Another limitation is the lack of control arm. However, the rates of response to placebo in
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59 patients with severe and resistant ulcerative colitis in randomized control trials are low,
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3 ranging from 10 to 33% at short term and from 6.6 to 14% in the long term.^{20, 29} In addition,
4
5 only patients who had active disease despite treatment with conventional therapy, including
6
7 local aminosalicylate and corticosteroid therapy, were included in the study.
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9

10 Importantly, the median follow-up was 17 months. A long-term follow-up is required to
11
12 assess the sustained efficacy of medical treatment in refractory UP, which is known to relapse
13
14 frequently, and because refractory disease is more prone to having a complicated outcome.^{8, 9,}

15
16
17 ¹⁴ Furthermore, this was a multicenter study. Infliximab therapy is rarely used to treat UP in
18
19 clinical practice. By screening a total of 420 patients treated with anti-TNF therapy for
20
21 ulcerative colitis at 6 referral centers in France, we were able to identify and analyze the
22
23 data of 13 patients. Finally, because of the retrospective study design and the inherent bias in
24
25 interpreting clinical response on medical records, we decided to assess clinical response not
26
27 only by using the judgment of the treating physician but also by recording the presence or not
28
29 of objective Mayo criteria such as diarrhea and blood in the stools.^{30, 36} In addition, the
30
31 absence of rectal disorders was defined as the absence of all predefined items, namely stool
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33 urgency, incontinence, tenesmus and rectal pain.
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38 Collectively, our findings indicate that infliximab may be effective and safe in inducing and
39
40 maintaining a clinical response in patients with refractory UP. It is unlikely that a randomized
41
42 controlled trial will ever be carried out to evaluate the efficacy of infliximab in refractory UP.
43
44 However, because of the retrospective study design of our study and small sample size,
45
46 infliximab efficacy in treating ulcerative proctitis needs to be confirmed in larger prospective
47
48 studies. Pending these results, infliximab should be used only in patients with disease
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50 refractory to all available medications. The optimal drug regimen as well as the optimal
51
52 duration of treatment remain to be determined.
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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	Sigmoidectomy	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.

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

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