UNIVERSITAT DE BARCELONA

Estrategias de diagnóstico y tratamiento en la enfermedad inflamatoria intestinal

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Digestive Diseases and Sciences

ISSN 0163-2116

Dig Dis Sci
DOI 10.1007/s10620-016-4089-2

Springer

Dig Dis Sci
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ORIGINAL ARTICLE

Long-Term Follow-Up of Patients Treated with Infliximab for Ulcerative Colitis: Predictive Factors of Response—An Observational Study

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Received: 22 September 2015 / Accepted: 15 February 2016

Abstract
Aim To evaluate the early and long-term efficacy of infliximab in ulcerative colitis and to determine predictors of response and colectomy.
Methods This is an ambidirectional cohort study in a tertiary referral center including patients who started infliximab within 2005 and 2008 and monitored until 2014. Efficacy was evaluated by partial Mayo scores at weeks 2, 4, 8, 30, and 54. Long-term treatment maintenance with infliximab and colectomy requirements were recorded.
Results Fifty-three patients were included with a median follow-up of 69.5 months. Clinical remission at the time point assessments was 40.8, 47.2, 54.7, 54.7, and 49.1 %. At the time of maximal follow-up, the proportion of patients under infliximab maintenance was 24.5 %. A higher level of albumin (OR 1.4, CI 95 % 1.06–1.8; $p = 0.017$) was predictive of a higher remission rate at week 8. Concomitant immunomodulators beyond 6 months were predictive of infliximab's long-term maintenance (OR 15.8, CI 95 % 1.8–135.4; $p = 0.012$). Colectomy was required in 41.5 %. Factors associated with a higher rate of colectomy at week 54 were previous treatment with cyclosporine (OR 3.4, CI 95 % 1.2–9.7; $p = 0.012$), absence of response at week 8 (OR 10.3, CI 95 % 3.3–31.7; $p < 0.001$), and not receiving concomitant immunomodulators (OR 4.1, CI 95 % 1.8–9; $p = 0.002$). Colectomy rates within the first 54 weeks were closely dependent on the number of variables present: none (0 %), 1 (26.3 %), 2 (71.4 %), or 3 (100 %) of them (log rank <0.0001).
Conclusions Low albumin, previous treatment with cyclosporine, absence of a concomitant immunomodulator, and lack of response at week 8 negatively affected the efficacy of infliximab in ulcerative colitis.

Keywords Infliximab · Observational study · Treatment outcome · Ulcerative colitis

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Introduction

Ulcerative colitis (UC) is a relapsing inflammatory bowel disease that can be adequately treated with 5-aminosalicylic acid preparations in approximately half of all patients.

Published online: 26 February 2016

However, 7–22 % of patients suffer chronically active or steroid-dependent disease requiring immunosuppressors [1], 30 % develop steroid resistance, and nearly 25 % require hospitalization [2] for a severe flare. These patients face a poor prognosis with a complicated disease course and a high risk of colectomy [3, 4]. Treatment with the anti-TNFα antibody infliximab has proven to be effective in inducing and maintaining remission in moderate-to-severe UC [5] patients who fail or are intolerant to immunomodulators and in steroid-refractory severe UC [6], resulting in a reduction in colectomies [5, 6]. Nevertheless, over 1 year, only one-third of patients achieve a sustained response, and about one-fifth experience sustained remission [7]. Persistent colonic inflammation has been linked to adverse long-term disease outcomes [8, 9] and a higher risk of dysplasia [10]. Therefore, determining predictors of response to anti-TNFα therapy will greatly aid routine clinical practice in identifying the best candidates for this therapy.

Methods

This is an ambidirectional (retrospective and prospective) cohort study that included all patients diagnosed with UC and treated with at least one dose of infliximab starting within January 2005 and November 2008 at the Inflammatory Bowel Disease (IBD) Unit of a tertiary referral center and followed up prospectively until the end of the study in November 2014 or occurrence of colectomy. Data were obtained from a local registry of patients with IBD that were included in the Spanish ENEIDA database ("Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales"). All patients participating in ENEIDA authorized the use of their clinical data for investigation. The decision for starting infliximab was based on previous and concomitant medications but was also based on the severity of the disease activity according to the subjective assessment of the treating physician. A formal calculation of disease activities indices was not used to start infliximab therapy.

Demographic data, disease characteristics, prior and concomitant therapies, clinical data at the time of infliximab initiation and response, as well as adverse events, were recorded. Disease extent was categorized according to the Montreal classification system, taking into account the maximum documented extension that occurred at any time during the course of the disease. Clinical activity was evaluated according to the Mayo score. Endoscopic disease severity was assessed according to the endoscopic Mayo subscore, based on the most severe lesions observed in any segment during sigmoidoscopy or full colonoscopy. Clinical response to treatment was assessed at all time points using the partial Mayo score. Remission was defined as a partial Mayo score ≤ 1, and response was defined as a decrease in the score ≥ 3 points and ≥ 30 % from baseline plus a drop in the rectal bleeding subscore ≥ 1 or an absolute rectal bleeding subscore of 0 or 1. The endpoints assessed were efficacy of infliximab at weeks 2, 4, 8, 30, and 54 in terms of response, remission and colectomy requirements, and determine predictors of these outcomes. After week 54, patients were followed as clinically indicated. Other endpoints assessed were the long-term efficacy of infliximab, the occurrence of adverse events, and the need for switching to a second anti-TNFα.

All data were analyzed using statistical package SPSS version 17. Univariate and subsequently binary logistic regression analysis was applied for those variables having statistical significance to determine independent predictors of response, colectomy, and long-term maintenance with infliximab. Kaplan–Meier curves for survival time free of colectomy were calculated and compared using the log-rank test. Data are expressed as median and inter-quartile range (IQR) for quantitative variables. A percentage is used for qualitative variables. Odds ratio and 95 % confidence intervals were calculated when appropriate. Statistical significance was set at $p < 0.05$.

Results

Clinical Characteristics of Patients

From a total of 667 patients diagnosed with UC at the IBD Unit of Hospital Clinic, Barcelona, Spain, 53 who had been treated with infliximab were included in the current study. The demographic and clinical characteristics of these patients are given in Table 1.

Median disease duration at the start of infliximab therapy was 4 years (IQR 1.8–8.7). All patients had been previously treated with corticosteroids, 88.7 % (47/53) with immunomodulators, and 39.6 % (21/53) with cyclosporine (11.3 % during the current flare). Indications for starting infliximab included failure of previous immunomodulators in 69.8 % (37/53), intolerance to immunomodulators in 9.4 % (5/53), a severe flare resistant to cyclosporine in 11.3 % (6/53), and steroid-resistant flare in 9.4 % (3/53). Two patients initiated infliximab for other reasons: one patient naïve to immunomodulators with an associated rheumatological disorder who experienced a flare and one patient with long-term remission with thiopurines who suffered a flare after withdrawal of immunomodulators.

Thirty-five patients included in the study (66 %) were evaluated with endoscopy at the initiation of infliximab, 85.7 % (30/35) had an endoscopic subscore of 3, 11.4 %

Table 1 Demographic characteristics of patients included ($n = 53$)

Sex (male) (%)	27/53 (50.9)
Age at inclusion (years) (median) (IQR)	36.4 (28.7–46.6)
Disease duration (years) (median) (IQR)	4 (1.8–8.7)
Family history of IBD (%)	10/53 (18.9)
Previous appendicectomy (%)	0/53 (0)
Smoking status	
Never (%)	30/53 (56.6)
Ex-smoker (%)	18/53 (34)
Active (%)	5/53 (9.4)
Extra intestinal manifestations during current flare	
Joint (%)	6/53 (11.3)
Skin (%)	2/53 (3.8)
Others (%)	1/53 (1.9)
Disease extension (Montreal)	
Distal (E1) (%)	2/53 (3.7)
Left-sided (E2) (%)	22/53 (41.6)
Extensive (E3) (%)	29/53 (54.7)
Previous steroids (%)	53/53 (100)
Previous immunomodulators (%)	47/53 (88.7)
Duration of previous treatment with immunomodulators (months) (median) (IQR)	13 (1–35.9)
Previous cyclosporine (%)	21/53 (39.6)
Cyclosporine resistant (%)	6/21 (28.6)
CRP (mg/l) (median) (IQR)	1.2 (0.2–4.2)
ESR (mm/h) (median) (IQR)	25.5 (11.3–68)
Hb (g/l) (median) (IQR)	11.8 (11.2–13.7)
Albumin (g/l) (median) (IQR)	41 (37–44)
Baseline Mayo score	
Full (median) (IQR) ($n = 35$)	10 (9–11)
Severe (>10p)/moderate (6–10p) (%)	28.6/71.4
Partial (median) (IQR) ($n = 53$)	6 (6–7.5)
Severe (7–9p)/moderate (5–6p) (%)	45.3/54.7
Baseline Mayo endoscopic subscore ($n = 35$)	
Score = 3 (%) (n)	85.7 (30/35)
Score = 2 (%) (n)	11.4 (4/35)
Score = 1 (%) (n)	2.9 (1/35)
Interval (months) (median) (IQR) within endoscopy and initiation of infliximab	0.4 (0.09–3.2)

(4/35) had an endoscopic subscore of 2, and 2.9 % (1/53) had a subscore of 1. The median full Mayo score ($n = 35$) was 10 (IQR 9–11), and the partial Mayo score ($n = 53$) was 6 (6–7.5) at the initiation of infliximab. At the time infliximab was started, 73.6 % (39/53) of patients were receiving concomitant treatment with steroids, although this was not related to a more severe disease [median full Mayo score of 10 (IQR 9–11) and 9.5 (IQR 8.8–10.3) in patients treated and not treated with steroids ($p =$ ns)] and 84.9 % (45/53) were on immunomodulators. The infliximab therapy consisted of 5 mg/kg at weeks 0, 2, and 6 for induction in all cases. No change in dose was introduced during induction period depending on the early response. Patients with clinical response at week 6 continued maintenance therapy every 8 weeks. Sixty-six percent (35/53) of patients completed the induction and initiated maintenance therapy, 15.1 % (8/53) received 3 doses of infliximab, 15.1 % (8/53) received 2 doses, and 3.8 % (2/53) received only 1 dose. The reasons for not completing the 3 induction doses with infliximab were lack of response in 8 of 10 cases, adverse event (abdominal septic shock) in 1 case, and infliximab treatment refusal after achieving remission after 2 doses in other case. Median follow-up time was 69.5 months (IQR 10.1–87.2).

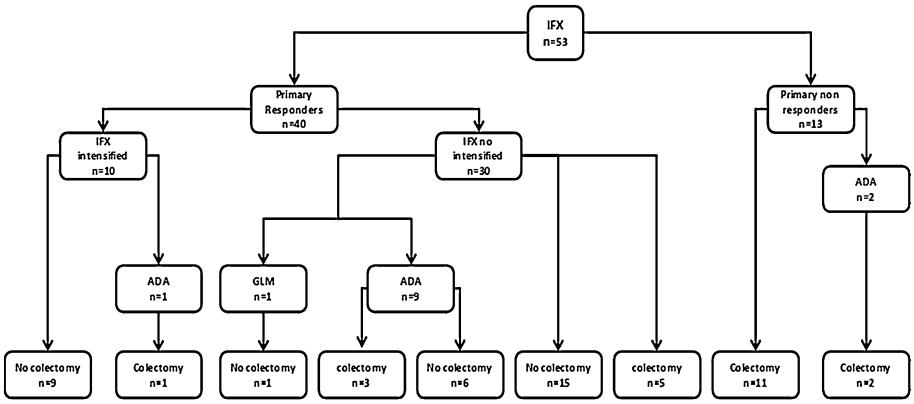

Fig. 1 Clinical outcomes of patients treated with infliximab, switch to anti-TNFα, and requirement of colectomy during the follow-up

Therapeutic Efficacy (Fig. 1)

Clinical Response

Using a last observation carried forward (LOCF) analysis for treatment failures, the proportion of patients responding to infliximab therapy at weeks 2, 4, 8, 30, and 54 were 60.4 % (32/53), 66 % (35/53), 75.5 % (40/53), 66 % (35/53), and 58.5 % (31/53), respectively. The proportion of patients achieving remission at these same time points were 37.7 % (20/53), 47.2 % (25/53), 54.7 % (29/53), 54.7 % (29/53), and 49.1 % (26/53), respectively. During this 54-week period, concomitant steroids were tapered and completely withdrawn in 53.8 % (21/39) of patients. The characteristics of patients who achieved clinical remission at week 8 are given in Table 2. Of the 29 patients who achieved clinical remission at week 8, 86.2 % (25/29) maintained sustained remission at week 30, while 75.9 % (22/29) did so at week 54. Treatment with infliximab was maintained for a median duration of 11 months (IQR 1.4–70.4). In addition, at the time of maximal follow-up [69.5 months (IQR 10.1–87.2)] the proportion of patients under infliximab maintenance therapy was 24.5 % (13/53). Intensification (defined as a dose increase to 10 mg/kg or a reduction in the interval between infusions to 6 or 4 weeks) due to secondary loss of clinical response was required in 18.9 % (10/53) of patients after a median of 6.7 months (IQR 5.5–13.9) of therapy with a regain of response occurring in 90 % (9/10) of cases.

Infliximab was withdrawn in 77.4 % (41/53) of patients after a median of 6.5 months (IQR 0.9–16). The main reasons for withdrawal included loss of response to infliximab that occurred after a median of 11 months (IQR 4.4–16.3) in 30.2 % (16/53) of patients and primary non-response in 24.5 % (13/53) of patients after a median of 0.6 months (IQR 0.5–1.8). Other less common reasons included the occurrence of adverse events in 11.3 % (6/53), treatment refusal in 3.8 % (2/53), and one patient (1.9 %) who achieved UC remission but persistence of arthralgias which compelled switch to methotrexate. Infliximab was stopped in 5.7 % (3/53) of patients for clinical sustained remission after a median of 76.2 months (IQR 59.1–87), 2 of whom maintained remission with thiopurines and one with mesalazine. A subgroup of 16.9 % (9/53) patients withdrawn infliximab for other different reasons (loss of response, adverse events, refusal of treatment, arthralgia), without change to a second anti-TNFα, and avoided surgery. Those patients maintained response with immunosuppressants (6/9), mesalazine (2/9), or no treatment (1/9). In order to determine predictive factors of remission in response to infliximab at weeks 2, 4, and 8, the following variables were analyzed: age, sex, disease duration, extension of disease, previous treatment with cyclosporine, CRP, albumin, baseline Mayo score, endoscopic subscore, and prior and concomitant therapies. More extended treatment with immunomodulators prior to initiation of infliximab and elevated albumin levels were variables associated with a higher remission rate due to infliximab at week 8, whereas concomitant therapy with immunomodulators was associated with a higher rate of remission at week 4 (OR 11.3, CI 95 % 1.1–120.1; $p = 0.04$) and week 8 (OR 15.6, CI 95 % 1.5–160.2; $p = 0.02$). In the multivariate analysis, a higher level of albumin was the only independent predictive factor of remission at week 8 (OR 1.4, CI 95 % 1.06–1.8; $p = 0.017$), whereas remission at week 8 was the only predictive variable for sustained remission at week 30 (OR 31.3, CI 95 % 6.9–140.8; $p < 0.001$) and week 54 (OR 13.3, CI 95 % 3.2–55.5; $p < 0.0001$). Median time infliximab treatment in responders and remitters at week 8, including those patients maintaining treatment at the end of follow-up, was 15.4 months (IQR 3.2–78.7) and 31.4 months (IQR 9.2–80.2), respectively ($p =$ ns). The estimated rate of withdrawal due to loss of response or the occurrence of an adverse event in responders at week 8 was 4.8 cases/100 patients/year. Concomitant immunomodulators beyond 6 months was the only independent predictive factor (OR 15.8, CI 95 % 1.8–135.4; $p = 0.012$) of long-term

Table 2 Comparison of patients achieving and not achieving clinical remission with infliximab therapy at week 8

	Remission ($n = 29$)	No remission ($n = 24$)	p
Age (years) (±SD)	39.2 (14.3)	37 (14.2)	ns
Sex (male) (%) ($n = 27$)	48.1 ($n = 13$)	51.9 ($n = 14$)	ns
Previous immunomodulators (%) ($n = 47$)	59.6 ($n = 28$)	40.4 ($n = 19$)	ns
Duration of previous treatment with immunomodulators (months) (median) (IQR)	22.6 (4.8–57.9)	8.9 (1–17.9)	$p = 0.05$
Cyclosporine ($n = 21$) (%)			
Previous flare ($n = 15$)	53.3 ($n = 8$)	46.7 ($n = 7$)	ns
Current flare, resistant ($n = 6$)	50 ($n = 3$)	50 ($n = 3$)	ns
Baseline Mayo score			
Full (median) (IQR) ($n = 35$)	9 (8.5–10.5)	10 (9–11)	
Severe (>10p)/moderate (6–10p) (%)	40/52	60/48	
Partial (median) (IQR) ($n = 53$)	6 (6–7)	7 (6–8)	
Severe (7–9p)/moderate (5–6p) (%)	45.8/62.1	54.2/37.9	ns
Endoscopic subscore (median) (IQR) ($n = 35$)	3 (3)	3 (3)	ns
Concomitant treatment with immunomodulators (%) ($n = 45$)	62.2 ($n = 28$)	37.8 ($n = 17$)	$p = 0.009$
Concomitant steroid therapy (%) ($n = 39$)	48.7 ($n = 19$)	51.3 ($n = 20$)	ns
Disease extension (%)			
Distal ($n = 2$)	100 ($n = 2$)	0	
Left-sided ($n = 22$)	54.5 ($n = 12$)	45.5 ($n = 10$)	
Extensive ($n = 29$)	51.7 ($n = 15$)	48.3 ($n = 14$)	ns
CRP (mg/l) (median) (IQR)	0.7 (0.1–3.6)	2.4 (0.5–5)	ns
Hb (g/l) (median) (IQR)	12.4 (10.9–14.3)	11.6 (10.7–12.9)	ns
Albumin (g/l) (median) (IQR)	44 (40.5–47.3)	37 (31–41.5)	$p < 0.001$

maintenance of infliximab with a median of 51.9 months (IQR 14.3–88.1) compared to 10.6 months (IQR 2.7–40.6) in patients who received immunomodulators less than 6 months.

Colectomy

Colectomy was required in 41.5 % (22/53) of patients after a median of 8.3 months (IQR 1.8–24.9). The characteristics of patients requiring colectomy are given in Table 3.

The proportion of patients requiring colectomy at weeks 2, 4, 8, 30, and 54 were 1.9, 5.7, 11.3, 18.9, and 24.5 %, respectively (Fig. 2). All primary non-responders (24.5 %; 13/53) underwent a colectomy after a median time of 8.6 weeks (IQR 4.5–63.5). 36.4 % (4/11) of responders underwent a colectomy after a median time of 66.7 weeks (IQR 31.7–136.9) compared to 17.2 % (5/29) of remitters who required a colectomy after a median time of 110 weeks (IQR 53.7–222.1) ($p = 0.036$).

At week 54, patients previously treated with cyclosporine (21/53), even in a previous flare (OR 3.4, CI 95 % 1.2–9.7; $p = 0.012$), patients who did not respond to infliximab at week 8 (13/53) (OR 10.3, CI 95 % 3.3–31.7; $p < 0.001$), or patients who did not receive concomitant immunomodulators (8/53) (OR 4.1, CI 95 % 1.8–9; $p = 0.002$) were at a higher risk of colectomy. These associations lost strength at the end of follow-up.

Within the first 54 weeks, none of the patients without any risk factor (0/24), 26.3 % (5/19) of those with 1 risk factor, 71.4 % (5/7) with 2 risk factors, and 100 % (3/3) with 3 risk factors required colectomy. During the long-term follow-up, surgery was necessary in all patients (7/7) with 2 risk factors and 52.6 % (10/19) of patients with 1 risk factor. Combinations of these variables facilitated an accurate prediction of colectomy in the early and long-term follow-up stages (log rank <0.0001) in a survival time analysis (Fig. 3). Colectomy was required earlier when more risk factors were present. All patients with all 3 risk factors underwent colectomy before week 4 (median 2.5, IQR 1.9–3.7), whereas the median was 24.4 weeks (IQR 7.1–79.7) and 51.1 weeks (IQR 19.3–178.7) for patients with two and one risk factor, respectively. The 2 patients without risk factors who underwent colectomy did so after 1 year (66.7 weeks) and 2 years (week 110).

Switch to a Second Anti-TNFα

Of 53 patients, 12 (22.6 %) switched from infliximab to adalimumab after a median time of 16.7 months (IQR 9–22.3): 9 of them due to a loss of response to infliximab, 2 due to the primary non-response, and one due to an adverse

Table 3 Comparison of patients treated with infliximab requiring and not requiring colectomy

	Colectomy ($n = 22$)	No colectomy ($n = 31$)	p
Age (mean) (SD)	37.4 (17.2)	38.4 (11.4)	ns
Sex (male) ($n = 27$)	37 ($n = 10$)	63 ($n = 17$)	ns
Disease extension (%)			
Distal ($n = 2$)	50 ($n = 1$)	50 ($n = 1$)	
Left-sided ($n = 22$)	31.8 ($n = 7$)	68.2 ($n = 15$)	
Extensive ($n = 29$)	48.3 % ($n = 14$) ($n = 11$)	51.7 ($n = 15$)	ns
CRP (mean) (SD)	5.7 (5.6)	1.9 (3.3)	ns
Baseline Mayo score			
Full (median) (IQR) ($n = 35$)	10 (9–11)	10 (9–11)	
Severe (>10p)/moderate (6–10p) (%)	30/36	70/64	
Partial (median) (IQR) ($n = 53$)	7 (6–8)	7 (6–8)	
Severe (7–9p)/moderate (5–6p) (%)	29.2/51.7	70.8/48.3	ns
Concomitant treatment with immunomodulators (%) ($n = 45$)	33.3 ($n = 15$)	66.7 ($n = 30$)	$p = 0.004$
Cyclosporine ($n = 21$) (%)			
Never ($n = 32$)	28.1 ($n = 9$)	71.9 ($n = 23$)	
Previous flare ($n = 15$)	60 ($n = 9$)	40 ($n = 6$)	
Current flare, resistant ($n = 6$)	66.7 ($n = 4$)	33.3 ($n = 2$)	$p = 0.049$
Concomitant steroid therapy ($n = 39$)	51.3 ($n = 20$)	48.7 ($n = 19$)	ns
Efficacy of infliximab at week 8			
Remission ($n = 29$)	17.9 ($n = 5$)	82.8 ($n = 24$)	
Response ($n = 11$)	36.4 ($n = 4$)	63.6 ($n = 7$)	
No response ($n = 13$)	100 ($n = 13$)	0	$p < 0.001$

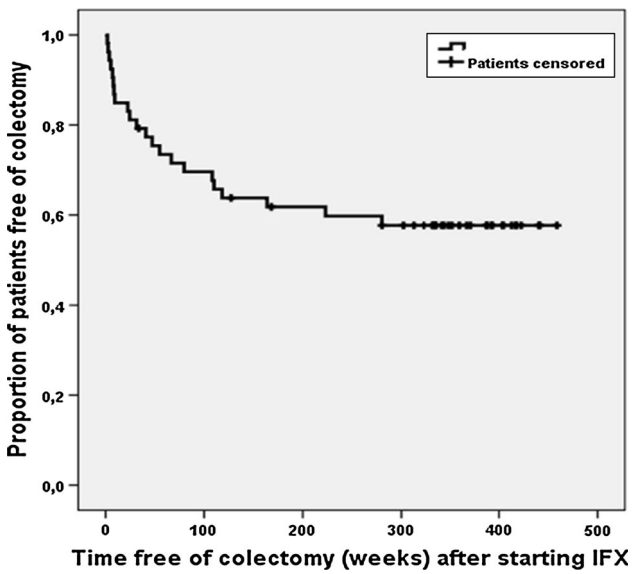

Fig. 2 Colectomy-free survival curve after starting infliximab

event (psoriasis). Among those patients treated with adalimumab, 5 regained response and 4 achieved remission. During follow-up, 66.7 % (6/9) of patients were taken off adalimumab and 44.4 % (4/9) underwent colectomy. Among the 3 patients with primary failure to adalimumab, 2 required colectomy, while 1 patient, who refused surgery, regained response after reintroduction of infliximab with intensified doses. One patient who lost response to infliximab after 89.8 months received golimumab as a second anti-TNFα and achieved clinical remission. Previous response to infliximab influenced the response to a second anti-TNFα: remitters, responders, and primary non-responders to infliximab achieved remission in 50 % (4/8), 33.3 % (1/3), and 0 % (0/2), respectively, after switching to a second anti-TNFα (p = ns).

Dysplasia and Colorectal Cancer

During follow-up, 50 % (12/24) of patients underwent chromoendoscopy for screening of dysplasia, and 16.7 % (2/12) presented low-grade dysplasia on an endoscopically visible lesion, with no subsequent development of cancer or need for colectomy.

Adverse Events

Twenty-two adverse events were recorded in 30.2 % (16/53) patients, most being infections. One patient suffered a

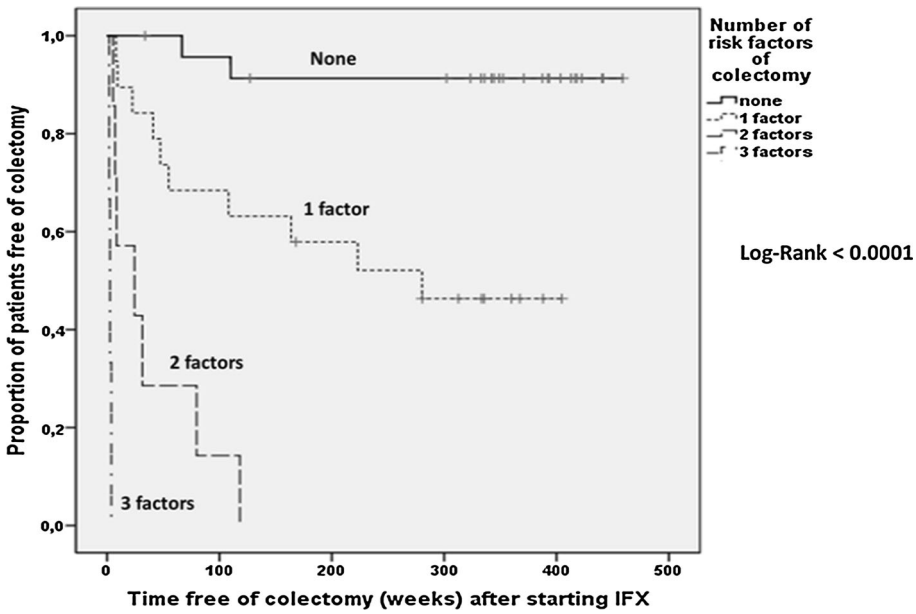

Fig. 3 Colectomy-free survival curve according to the presence of colectomy risk factors. Risk factors: previous cyclosporine, concomitant immunomodulators, lack of response to infliximab at week 8

serious adverse event, an abdominal septic shock related to a severe flare, which required admission at the intensive care unit. After the infection was resolved, remission was achieved with cyclosporine although a colectomy was required during follow-up. Two patients were diagnosed with tuberculosis. The first patient developed renal tuberculosis despite appropriate treatment of latent tuberculosis following a positive PPD skin test and a normal chest X-ray. The second patient developed pulmonary tuberculosis 1 year after starting infliximab. Previous screening of latent tuberculosis for this patient was negative. Infliximab was stopped, and the infection was resolved with anti-tuberculous therapy. Three months later, the patient was diagnosed with a cerebral abscess that was adequately managed with broad-spectrum antibiotics. Two patients presented a community-acquired pneumonia that required hospitalization; both were resolved with intravenous antibiotic therapy. Infliximab was stopped temporarily, with uneventful reintroduction after resolution of the infection. Infliximab was permanently withdrawn in 6 patients (11.3 %): the patient who suffered abdominal sepsis, the two patients with tuberculosis, one patient who suffered two acute infusion reactions plus a cutaneous fungal infection and tonsillitis, one patient who presented recidivant skin abscesses and cutaneous herpes, and two patients who developed infliximab-related psoriasis and toxicoderma. No deaths occurred during the study.

Discussion

This observational study addressed the efficacy of infliximab therapy in clinical practice involving long-term follow-up and identified predictors of response that can be easily assessed. Since the first publication of pivotal clinical trials that led to registration of the drug for the treatment of UC, some concerns have been raised regarding the efficacy of this therapy in clinical practice. The ACT trials [5] included 728 moderate-to-severe UC patients and evaluated the efficacy of infliximab compared to placebo for the induction and maintenance of remission. Remission and response were achieved at week 8 in 38.8 and 69.4 % in ACT1 and 33.9 and 64.5 % in ACT2, respectively, using an infliximab dose of 5 mg/kg. At week 30, the rates of remission and response were 33.9 and 52.1 % in ACT1 and 25.6 and 47.1 % in ACT2, and at week 54 the rates were 42 and 55 % in ACT1. Compared with these results, the current study observed a higher proportion of patients achieving response and remission under infliximab therapy. The reasons for this higher response rate in clinical practice, compared to clinical trials, may be diverse and could include optimization of drug dosing, with intensification of therapy in patients who presented loss of response during follow-up, and concomitant use of immunomodulators, which in the current study doubled the proportion of patients under combination therapy compared to the ACT trials. It is not likely that disease severity was a cause for the increased response in this study, since the full Mayo score at baseline (median 10) was even higher than that in the ACT trials (ACT1 8.4, ACT2 8.5) in endoscopically assessed patients. Another factor that might have led to inflated estimates of responders was the lack, in the majority of cases, of an objective measure of disease activity such as endoscopy or instead calprotectin as a surrogate marker of inflammation, during follow-up. In any case, a high correlation between full and partial Mayo scores was uniformly observed [11], and mucosal healing

seems to be a consequence in responders. There are not recommendations in international guidelines neither studies about modifications of therapy in clinical remitters based on mucosal activity detected by endoscopy.

Previous observational studies in tertiary referral centers that assessed the efficacy of infliximab in clinical practice have produced similar results to the current observational study. Ferrante et al. [12] evaluated the efficacy of infliximab in 100 patients with moderate-to-severe UC treated with 1 or 3 dose of infliximab 5 mg/kg. The median follow-up was 2.7 years. At week 4, 65 % of patients achieved response and 41 % were in remission. These results are comparable to our study in terms of efficacy. However, among the 100 patients included, 42 had already participated in the ACT1 trial and had been treated with infliximab, which could imply a bias of selection in favor of responders. On the other hand, not all patients received the standard induction and maintenance scheme, and only 63 % of the patients received concomitant treatment with immunomodulators, which was also proportionally lower to that in the current study (85 %).

In our study, longer prior treatment with immunomodulators and combination therapy were associated with a higher probability of remission at week 8. In addition, albumin levels were an independent predictive factor of response. Lack of response to infliximab has been previously associated with disease severity [13, 14], elevated CRP [5, 15], low albumin and hemoglobin levels [16], and extensive colitis [17]. A growing body of evidence supports the notion that combination therapy with infliximab and thiopurines is superior to monotherapy with infliximab [18–20] in UC. In the SUCCESS trial [18], patients with moderate-to-severe UC and who were naive for immunomodulators and followed up during 16 weeks were included. Combination treatment with infliximab and immunosuppressors proved superior to monotherapy with either immunomodulators or anti-TNFα alone in achieving steroid-free remission. More recently, a study [20] involving 126 patients with UC followed for 12 months showed that concomitant therapy with thiopurines was an independent predictor of sustained clinical response to infliximab (HR 3.98; 95 % CI 1.73–9.14). Our study has shown not only that infliximab fails in two-thirds of patients during long-term follow-up, but also supports the concept that the use of immunomodulators, even after previous failure, increases the long-term efficacy of infliximab.

Colectomy is undoubtedly the most relevant clinical outcome for UC. The efficacy of infliximab in preventing colectomy was already shown in the ACT studies [5]; it was required in 9.5 % of patients treated with infliximab compared with 14 % in those who received a placebo ($p = 0.035$). The only randomized placebo-controlled study in patients with steroid-refractory UC [6] showed that the percentage of colectomy cases within the first 3 months after a single infliximab infusion was 29 % compared to 67 % in the placebo group. In the CYSIF study, which compared infliximab and cyclosporine [21] for steroid-refractory UC, 21 % (12/57) of patients underwent colectomy within the first 98 days after starting infliximab. In the current study, we observed a higher proportion of patients requiring surgery during the first year compared to the ACT pivotal studies [5], though similar to the observational study of Ferrante et al. [12]. Moreover, and importantly, we could identify predictors of colectomy. Combination therapy with immunomodulators, even after a previous failure, reduced the risk of surgery, whereas prior therapy with cyclosporine and a lack of response to infliximab at week 8 increased the risk of colectomy. Disease severity, elevated CRP [7, 13, 15], colitis lasting $\leq$3 years [5], and previous intravenous steroids or cyclosporine treatment [7] have been described as predictive of colectomy. For the subgroup of patients previously treated with cyclosporine, our results are in line with those published by Chaparro et al. [22], who described that concomitant treatment with immunomodulators was the only predictive factor of response to infliximab in a cohort of 47 UC steroid-resistant patients who failed to respond to cyclosporine (HR 9.8, CI 95 % 1.2–78; $p = 0.03$). The strength of our study resides in the long-term follow-up, revealing that infliximab treatment helped avoid colectomy in three quarters of responders, one-quarter of these after the rescue by a second anti-TNFα. Moreover, our results support the need for alternative therapies that utilize a different mechanism of action.

Finally, in our series the onset of adverse events (30 %) led to drug discontinuation in only 11.3 % of patients, although it should be noted that some of them were severe (tuberculosis, brain abscess). The ACT [5] trials described serious adverse events with placebo, infliximab 5 mg/kg, and infliximab 10 mg/kg in a 25.6, 21.5, and 23.8 % of patients, respectively, in the ACT1 trial and 19.5, 10.7, and 9.2 % in the ACT2 trial. In our study, the only relevant adverse events captured were those based on the judgment of the treating physician. The higher rate of severe adverse events observed in our study compared to the ACT trials might be related to the accumulated risk of long-term exposure to infliximab. Limitations of the study include the lack of objective measures of efficacy, such as endoscopy, as previously mentioned or the measurement of trough levels of infliximab for adjustment of doses, which were not available at the time the study was started. There is no consensus about therapeutic through levels of infliximab and optimal measurement technique in UC. Also, trough levels are not widely available, their role in management is not clearly established, and recommendations about their use in clinical practice are lacking.

In summary, the current observational study not only further supports the use of combination therapy, even after immunomodulators have failed, in all UC patients whose disease course warrant infliximab treatment, but also identifies a subgroup of patients at higher risk of early surgery who would benefit from closer monitoring.

Acknowledgments The authors acknowledge Joe Moore for editorial assistance.

Funding This work has not received any financial support.

Compliance with ethical standards

Conflict of interest OGB, IO, and MS have received lecture fees from Abbvie and MSD; MA has received lecture fees form Abbvie; JP has received consultant fees from Abbvie and MSD and research grant from Abbvie; ER has received consultant and lecture fees from Abbvie and MSD. FF and JE have no conflict of interest.

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