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DOI: 10.17235/reed.2020.6688/2019
Link: PubMed (Epub ahead of print)

Please cite this article as:
Ramos Laura, Hernández Camba Alejandro, de la Barreda Heusser Raquel, Vela Milagros, Alonso-Abreu Inmaculada, Rodríguez G. Esther, Carrillo Marta, Tardillo Carlos, Rodríguez Yolanda, Figueroa Marrero Andrés, Ceballos Daniel, Cruz Noelia, Kolle-Casso Lilian , Jiménez Sosa Alejandro . Predictive factors of clinical response to treatment with anti-TNF agents in ulcerative colitis: what have we learned from our patients?. Rev Esp Enferm Dig 2020. doi: 10.17235/reed.2020.6688/2019.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

OR 6688 inglés

Predictive factors of clinical response to treatment with anti-TNF agents in ulcerative colitis: what have we learned from our patients?

Laura Ramos[1], Alejandro Hernández-Camba[2], Raquel De la Barreda[1], Milagros Vela[2], Inmaculada Alonso-Abreu[1], Esther Rodríguez G.[2], Marta Carrillo-Palau[1], Carlos Tardillo[2], Yolanda Rodríguez[2], Andrés Figueroa-Marrero[3], Daniel Ceballos[3], Noelia Cruz[4], Lilian Kolle-Casso[5] and Alejandro Jiménez[6]

[1]Department of Digestive Diseases. Hospital Universitario de Canarias. Santa Cruz de Tenerife, Spain. [2]Department of Digestive Diseases. Hospital Universitario Nuestra Señora de Candelaria. Santa Cruz de Tenerife, Spain. [3]Department of Digestive Diseases. Hospital Universitario Dr. Negrín. Las Palmas de Gran Canaria, Spain. [4] Department of Digestive Diseases. Hospital José Molina Orosa. Lanzarote, Spain. [5] Department of Digestive Diseases. Hospital General de La Palma. La Palma, Spain. [6] Research Unit. Hospital Universitario de Canarias. Santa Cruz de Tenerife, Spain

Laura Ramos and Alejandro Hernández-Camba contributed equally to the present study.

Received: 28/10/2019

Accepted: 09/01/2020

Correspondence: Laura Ramos López. Department of Digestive Diseases. Hospital Universitario de Canarias. Ctra. Ofra, s/n. 38280 La Laguna, Santa Cruz de Tenerife. Spain

e-mail: laura7ramos@gmail.com

Author´s contribution: Laura Ramos and Alejandro Hernández-Camba have contributed equally in this study.

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Conflicts of interest: LR: educational and travel grants, speaker fees from MSD, Pfizer, Abbvie, Takeda, Janssen, Shire Pharmaceuticals, Ferring and Dr. Falk Pharma. AHC: educational and travel grants, speaker fees from Pfizer, Abbvie, Takeda, Janssen, Ferring, Tillots Pharma and Kern Pharma. The remaining authors declare no conflicts of interest in relation to the present study.

ABSTRACT

Introduction: inhibitors of tumor necrosis factor alpha (anti-TNFs) are effective drugs for the treatment of moderate-to-severe ulcerative colitis (UC). However, many patients do not respond or lose therapeutic response during follow-up.

Objectives: to analyze the determining factors of clinical response to anti-TNFs in UC.

Methods: a multicenter retrospective study was performed in 79 patients with UC who started treatment with anti-TNFs between 2009 and 2015. The primary endpoint was clinical remission (pMayo index ≤ 1) at 12 months. Furthermore, remission and clinical response (final pMayo score ≤ 3) and corticoids discontinuation were assessed at three, six and 12 months. An analysis was performed to identify variables predictive of clinical response.

Results: at 12 months, remission and clinical response were seen in 59.2 % and 77.8 % of patients, respectively. Corticoids could be discontinued in 82.4 % of patients. At 12 months, corticoids discontinuation (< 3 months) (OR 0.06; 95 % CI: 0.01-0.24) and clinical response at six months (OR 0.008; 95 % CI: 0.001-0.053) were independent factors predictive of clinical remission.

Conclusion: in patients with active UC on anti-TNFs, corticoid discontinuation within three months and clinical response at six months after treatment onset are predictive of clinical disease remission.

Keywords: Ulcerative colitis. Biologic drugs. Anti-TNF. Adalimumab. Infliximab.

INTRODUCTION

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory bowel disease (IBD) that affects the colonic mucosa and manifests with clinical activity (flare-ups) and remission

phases (1-3). UC therapy is aimed at reducing colonic mucosal inflammation to relieve symptoms (induction therapy) and avoid further flare-ups and their complications (maintenance therapy) (4). Tumor necrosis factor alpha inhibitors (anti-TNF) are used for moderate-severe UC refractory to corticosteroid therapy (corticosteroid-refractory UC) or corticosteroid-dependent UC (5). Its inclusion in the therapeutic armamentarium against UC (infliximab [IFX] since 2006, adalimumab [ADA] since 2012 in Spain) has managed to reduce hospitalization rates and the need for surgery in these patients (6). Data are available from the pivotal studies of anti-TNF drugs that showed clinical remission in 34.7 % and clinical response in 45.5 % of subjects at 54 weeks. Data collected from clinical practice studies during the last decade continued to show remission rates of 40-50 % and clinical response rates of 60-70 %, within the first year of treatment with anti-TNFs (7). However, there is a significant proportion of patients who will not respond to anti-TNF therapy (primary failure) or will lose their response to anti-TNF agents (secondary failure), to the extent of eventually needing a colectomy. Vedolizumab, a humanized monoclonal antibody that specifically binds α4β7-integrin and is expressed by helper T-cells that migrate to the gastrointestinal (GI) tract, was added to this set of treatments for UC in 2014. Tofacitinib, an inhibitor of Janus kinases (JAK), was also added in 2018. JAK inhibitors (JAKIs) are categorized as small-molecule drugs presently used in the second line of treatment after anti-TNF failure, providing their use is not contraindicated (8).

Therefore, the goal of this study was to assess the long-term effectiveness of anti-TNF agents in patients with UC, and to identify factors associated with effectiveness in a real clinical practice setting to facilitate decision-making for the management of these patients.

MATERIALS AND METHODS

Experimental design

A retrospective, multicenter, observational study was performed in patients diagnosed with UC who received anti-TNF therapy from January 2009 to December 2015, according to the hospital pharmacy records in each of the five participating sites. The study was approved by the Clinical Research Committee at the Hospital Universitario

de Canarias (2015-72).

Patients and endpoints

Subjects were diagnosed with UC based on clinical, endoscopic and histologic criteria at least within the previous six months, with follow-up ≥ 12 months at the Gastroenterology Outpatient Clinic after anti-TNF therapy onset. Demographic data, UC extension per Montreal criteria, year of diagnosis, corticosteroid use, and/or hospital admissions within six months after diagnosis, time to therapy onset, type of biologic therapy (IFX or ADA), change of biologic during follow-up, concomitant medication (immunomodulators or corticosteroid cycles), hospital admissions and/or need for colectomy during follow-up were all recorded. Adverse events and discontinuation and/or restart of biologic therapy during follow-up were also collected.

The primary endpoint of the study was to assess the proportion of patients in clinical remission at 12 months after treatment onset with anti-TNF biologic drugs. Secondary endpoints included an assessment of clinical remission at three and six months, clinical response at three, six, and 12 months and corticosteroid discontinuation at these same time points. Clinical remission was defined as a partial Mayo (pMayo) index ≤ 1 point, with a rectorrhagia subscore of 0. Clinical response was defined as a decrease ≥ 3 in the pMayo score. Treatment failure was established in cases of corticosteroid indication, failed corticosteroid discontinuation, need for hospital admission and/or surgery for active disease during anti-TNF therapy.

Inflammatory activity was assessed with C-reactive protein (CRP) and fecal calprotectin (FC) levels at treatment onset and at three, six, and 12 months, when available.

Statistical analysis

A descriptive statistical analysis was performed of the sociodemographic and clinical data collected. Mean and standard deviation values were used for continuous variables, and frequencies were used for qualitative variables. Results were plotted to facilitate interpretation. Based on the study goals, each variable was assessed and then compared in a univariate manner to the response variables established in the protocol,

in order to identify the potential factors predictive of therapy response and no response. Subsequently, multivariate logistic regression models were used with the variables that achieved statistical significance and adjustments were made for the results obtained. Treatment maintenance was studied with Kaplan-Meier survival curves to assess the median survival time and to analyze the mean value obtained. Then, a Cox multivariate regression was used to establish potential predictive factors for the study outcome. Logistic regression results are shown as odds ratios (OR) and 95 % confidence intervals (CI), both for univariate and multivariate analyses. Statistical significance was considered at $p < 0.05$. All the analyses were performed using the IBM SPSS statistics v.21 software.

RESULTS

Demographic and clinical data regarding ulcerative colitis

A total of 79 patients with UC were included from five hospitals in the Canary Islands (Spain). Demographic data and baseline patient characteristics are shown in table 1. A total of 58 patients (73 %) received IFX and 21 (27 %) received ADA. The time from diagnosis to anti-TNF therapy onset was 61 months (SD: 75). Only 3.7 % (3/79) of patients had previously received an anti-TNF agent.

Assessing clinical response to biologic therapy

Clinical results are summarized in figure 1. Clinical remission was seen in 59.2 % of subjects, with a clinical response and corticosteroid discontinuation in 77.8 % and 82.4 % of patients at 12 months, respectively. At three months after treatment, clinical remission was reached by 48.1 %, with treatment response in 67.1 % and corticosteroids discontinuation in 68.9 % of subjects. At the six-month cutoff, clinical remission was 57.9 %, with response and steroid discontinuation in 76.9 % and 70.4 %, respectively.

Thirty percent of patients required a change of biologic (from IFX to ADA or vice versa). Biologic therapy discontinuation during follow-up was seen in 41 % (32/79) of patients, primarily because of no response (primary failure) in 40.6 % (13/32) of cases, or clinical and/or endoscopic remission in 28 % (9/32) of patients. Loss of response (secondary

failure) was observed in 9.4 % (3/32) of cases and led to treatment discontinuation after a median of 14 months (SD: 23). In 34 % of these patients (11/32), biologic therapy was reinstated mainly because of corticosteroid dependency (8/11, 73 %), and clinical response was obtained in 50 % of cases during follow-up. The mean anti-TNF therapy duration and follow-up was 29 months. The proportion of patients who stayed on anti-TNF therapy during the whole follow-up period is shown in figure 2.

Assessment of inflammatory activity biomarkers

Anti-TNF therapy significantly reduced CPR levels from baseline at three, six, and 12 months (2.1, 1.2, and 0.85 *vs* 4.6 mg/dl; p = 0.004, respectively). Furthermore, there was a significant reduction in FC levels at three and 12 months from baseline (172 and 219 *vs* 357 µ/g; p = 0.009, respectively).

Safety

Side effects occurred in 20 % (16/79) of patients (ten psoriasis-like lesions, three IFX infusion-related reactions, one sepsis with pulmonary origin, one rhinopharyngitis, and one pneumonitis) and led to treatment discontinuation after the adverse event in only seven (8.8 %) of these cases.

Colectomies

During the overall follow-up period, eleven colectomies (14 %) were performed, without reaching the median survival time. None of the studied factors were associated with the incidence of colectomies in a statistically significant manner.

Predictors of clinical effectiveness

No differences were found in clinical effectiveness according to treatment type (IFX or ADA), anti-TNF therapy indication, or the use of immunomodulators prior to or during biologic therapy. Neither CRP nor FC inflammation markers were significantly associated with treatment response in our series.

According to the univariate analysis, the variables associated with poor response to anti-TNF therapy included hospitalization within six months of treatment (OR 3.75; 95

% CI: 1.16-12.09; p < 0.05); requiring a change of biologic during follow-up (OR 6.11; 95 % CI: 1.84-20.22; p < 0.01) and requiring > 1 corticosteroid cycle during biologic therapy (OR 1.54; 95 % CI: 1.17-2.01; p < 0.01) (Table 2).

The multivariate analysis showed that concomitant treatment with corticosteroids was independently associated with no response to anti-TNF therapy (OR 1.51; 95 % CI: 1.16-1.98; p < 0.01). The failure risk increased by 1.5-fold with each corticosteroid cycle administered within the first 12 months of biologic therapy (Table 3).

The multivariate analysis also showed that the sole independent variable predictive of a positive response to anti-TNF therapy was corticosteroid discontinuation at three months after biologic therapy onset (OR 0.07; 95 % CI: 0.01-0.32; p < 0.001) (Table 3).

DISCUSSION

The availability of anti-TNF biologic therapies for ulcerative colitis represents a significant shift in the management of these patients. This multicenter, retrospective series that used anti-TNFs for moderate and severe UC has shown that these medications are safe and effective to induce and maintain remission and clinical response after one year of follow-up. Furthermore, predictive factors for treatment effectiveness were identified, which may help to identify patients at high risk for anti-TNF therapy failure earlier, so that other treatment options can be considered.

In pivotal studies, the long-term assessment of IFX (studies ACT 1-2) showed a clinical response in 45.5 % and clinical remission in 35 % of cases at 54 weeks (9). Regarding ADA, clinical response and remission in clinical trials (ULTRA 1-2) was seen in 30.2 % and 17.3 % of cases, respectively (10). In our series, the overall remission rate, including both IFX and ADA, was 59.2 % of cases using the very stringent criterion, namely the pMayo index score lower than or equal to 1 point. A clinical response rate of 77.8 % at 12 months was obtained, with an effective corticosteroid discontinuation rate of 82.4 % over this follow-up period. Patients with extensive (E3, 51.9 %) and left-sided (E2, 45.6 %) colitis for a long time prior to anti-TNF therapy onset (median, 61 months; SD: 75) were included in our series, with the use of immunomodulating agents in up to 86 % of cases. This population better reflects a real-world clinical practice cohort as compared to pivotal trials, since the results reported by real-world studies are similar to those seen in our series, with higher remission and response rates

compared to clinical trials (11). Ferrante et al. reported their experience at a Belgian center in 121 individuals followed up for a mean of 33.4 months, with a clinical response (at any time point during follow-up) in 68 % of patients (12). The French experience was reported in a five-center study of data collected from 2000 to 2009 in 191 subjects, with a clinical response obtained in 55.7 % of the cohort during a mean follow-up of 18 months (13). Armuzzi et al. reported the clinical effectiveness of anti-TNF therapy in 126 patients with corticosteroid-dependent UC at three Italian centers, showing steroid-free clinical remission in 46.8 % of cases at 12 months (14). In the aforementioned three studies, colectomy rates of 17 %, 18 %, and 9.5 %, respectively, were reported. Colectomy incidence in our series was similar, with a rate of 13.9 % (one third during the first year on anti-TNF therapy), but predictors of the need for surgery could not be established in the statistical analysis.

Previous clinical practice studies identified predictors of a good response to anti-TNF therapy, such as an early decrease in CRP levels, concomitant use of immunomodulators, ability to discontinue corticosteroids at six and 12 months and adequate anti-TNF blood levels without the development of anti-drug antibodies (12,14-17). In our study, significant predictors of clinical remission at 12 months included clinical response at six months on anti-TNF therapy (OR 0.10; 95 % CI: 0.002-0.067; $p < 0.001$) and the possibility of steroid discontinuation at three months after anti-TNF therapy onset (OR 0.07; 95 % CI: 0.01-0.29; $p < 0.001$). Furthermore, we identified the use of several biologics (change of anti-TNF drug, IFX to ADA or vice versa) (OR 6.11; 95 % CI: 1.84-20.22; $p < 0.01$) and the use of corticosteroid cycles during anti-TNF therapy (with risk increasing with each cycle; OR 1.54; 95 % CI: 1.17-2.01; $p < 0.01$) as risk factors for poor therapy response. Thus, patients starting anti-TNF therapy who exhibited risk factors and/or failed to meet their therapeutic goals may be candidates to change the medical treatment for other therapeutic targets.

The possibility to collect patient data from up to five sites is one of the strengths of the study as it eliminates the potential bias associated with a single center or investigator. We assume that all centers complied with the recommendations issued by the European Crohn's and Colitis Organisation (ECCO) and the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) concerning the management of

patients with UC with anti-TNF therapy. The retrospective nature of our review, the impossibility of endoscopic assessment and the unavailability of biomarkers (CRP and FC) in some cases did not allow an objective assessment of mucosal healing as an efficacy endpoint and represents a study limitation.

We know that up to 30 % of patients will fail to respond to anti-TNF therapy (primary failure) (18) and up to 50 % will lose their response over time (secondary failure) (19). The newer agents available for UC, such as vedolizumab and tofacitinib, will play a relevant role in this group of patients who are refractory to anti-TNFs (5,20-21). A better knowledge of both protective and risk factors in the use of anti-TNF drugs will allow us to identify patients who should maintain this therapy, and those where the therapeutic target should be changed.

In summary, our study confirms the effectiveness and safety profile of anti-TNF agents in the majority of patients with UC after 12 months of follow-up. Patients who failed to respond clinically at six months, or discontinued corticosteroids at three months on anti-TNF therapy, are likely poor responders to anti-TNF agents. Thus, other medical treatment options should be promptly considered for their management.

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Table 1. Patient characteristics

n: 79 patients	
Age (years): mean (SD)	43 (13.56)
Gender: female, n (%)	35 (44.3)
Weight (kg): mean (SD)	71.94 (15.08)
Height (cm): mean (SD)	169.83 (10.12)
Smoker, n (%)	4 (5.1)
Type of ulcerative colitis*, n (%)	
E1	2 (2.5)
E2	36 (45.6)
E3	41 (51.9)
Age at diagnosis: mean (SD)	34.63 (12.76)
Hospitalization within 6 months after diagnosis, n (%)	27 (34)
Corticoid use within 6 months after diagnosis, n (%)	49 (62)
Immunosuppressant use before anti-TNFs, n (%)	68 (86)
Duration of immunosuppressant use before anti-TNFs (months): mean (SD)	16.85 (27.03)
Admissions before anti-TNFs, n (%)	54 (68.3)
Number of GC cycles before anti-TNFs: mean (SD)	4.69 (6.93)
Anti-TNF indication, n (%)	
Corticosteroid-dependent	53 (67.1)
Corticosteroid-refractory	25 (31.6)
Ocular manifestations	1 (1.3)
Type of anti-TNF therapy, n (%)	
Infliximab	58 (73.4)
Adalimumab	21 (26.6)
Total follow-up duration (months): median (min-max)	30 (0.5-132)
GC use at anti-TNF therapy onset, n (%)	63 (79.7)
Time to anti-TNF therapy onset (months): mean (SD)	61.11 (75.9)

SD: standard deviation. *Montreal classification: E1, ulcerative proctitis; E2, left-side colitis; E3, extensive colitis.

Table 2. Multivariate study of factors associated with clinical remission at 12 months

Risk factors	*OR*	*95 % CI*		*p*
Hospitalization within 6 months of diagnosis	3.75	1.16	12.09	< 0.05
Change of biologic during follow-up	6.11	1.84	20.22	< 0.01
Number of corticoid cycles	1.54	1.17	2.01	< 0.01
Protective factors	*OR*	*95 % CI*		*p*
Corticoid discontinuation at 3 months	0.06	0.01	0.24	< 0.001
Corticoid discontinuation at 6 months	0.12	0.03	0.49	< 0.01
Response at 3 months	0.08	0.02	0.30	< 0.001
Response at 6 months	0.008	0.001	0.053	< 0.001
Clinical remission at 3 months	0.10	0.02	0.49	< 0.01
Clinical remission at 6 months	0.06	0.01	0.33	< 0.01
Duration of biologic drug use	0.95	0.91	0.99	< 0.05

OR: odds ratio; CI: confidence interval; p: probability value.

Table 3. Multivariate study of factors associated with clinical remission at 12 months

Risk factors	*OR*	*95 % CI*		*p*
Corticoid cycles	1.51	1.16	1.98	< 0.01
Protective factors	*OR*	*95 % CI*		*p*
Response at 6 months	0.10	0.002	0.067	< 0.001
Corticoid discontinuation at 3 months	0.07	0.01	0.29	< 0.001

OR: odds ratio; CI: confidence interval; p: probability value.

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Fig. 1. Clinical evolution during follow-up.

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Fig. 2. Kaplan-Meier curve showing anti-TNF maintenance during follow-up.