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Risk of colectomy in patients with ulcerative colitis under thiopurine treatment☆,☆☆

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Abstract

Background and Aims: Little is known about the risk factors of colectomy in patients with ulcerative colitis (UC) under thiopurine treatment. The aim of the study was to determine the prevalence and the predictive risk factors of colectomy in an extensive cohort of patients with UC treated with thiopurines in Spain.
Methods: Among 5753 UC patients, we identified those diagnosed between 1980 and 2009 and treated with azathioprine or mercaptopurine (AZA/MP). We analyzed the age at diagnosis, familial history of IBD, extraintestinal manifestations (EIMs), disease extent, smoking status and treatment requirements (AZA/MP, cyclosporine (CsA) or anti-TNFα). Colectomies for dysplasia or cancer were excluded. Survival analysis and Cox proportional hazard regression were performed. Results were reported as hazard ratios (HR) with 95% CI.
Results: Among the 1334 cases included, 119 patients (8.9%) required colectomy after a median time of 26 months (IQR 12–42) after AZA/MP initiation. Independent predictors of colectomy were: Extensive UC (HR 1.7, 95% CI: 1.1–2.6), EIMs (HR 1.5, 95% CI: 1.0–2.4), need for antiTNFα (HR 2.3, 95% CI: 1.5–3.4) and need for CsA (HR 2.4, 95% CI: 1.6–3.7). Patients requiring early introduction of AZA/MP had an increased risk of colectomy with a HR of 4.9 (95% CI: 3.2–7.8) when AZA/MP started in the first 33 months after UC diagnosis.
Conclusions: Nearly one-tenth of patients with UC under thiopurines require colectomy. Extensive UC, EIMs, need for CsA or anti-TNFα ever and an early need for AZA/MP treatment were associated with a higher risk of colectomy. These risk factors of colectomy could help to stratify risk in further controlled studies in UC.

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by diffuse mucosal inflammation limited to the colon.[1] UC treatment goals are to induce remission as rapidly as possible and to maintain remission on a long-term basis, in order to reduce complications, improve quality of life and avoid colectomy. Up to 22% patients with UC suffer from chronically active disease or steroid dependent disease.[2] Immunosuppressive (IMS) agents like purine derivates azathioprine (AZA) and mercaptopurine (MP) are recommended in a steroid-dependent scenario.[3] Despite the widespread use of AZA/MP, evidence on its efficacy is based on studies with a small number of cases. Two meta-analyses reported that AZA/MP treatment increases the absolute rate of maintained remission by 23%[4] with a number needed to treat of 4 patients[5] when compared to placebo.

Studies regarding colectomy risk in UC are heterogeneous in terms of disease activity, previous treatments, disease extent and demographics. This heterogeneity may account for some differences in reported rates of colectomy. In addition, improvements in treatment have most probably led to a progressive decrease in colectomy rates. While a 10-year colectomy risk was 25% in 1994,[6] colectomy rates have decreased in the last 15 years[7] and two recent population-based studies reported a 10-year cumulative risk of 8.7%–10.4%.[8,9]

Although surgery may be preferable to persistent severe disease refractory to medical treatment, it has a variable mortality and morbidity risks and it is associated to several short and long term postsurgical complications.[10–12] While most of the studies focused on the effectiveness of AZA/MP as a primary endpoint, regarding the maintenance of steroid-free remission, little is known about the risk factors of colectomy among patients under AZA/MP.

The aim of our study was to describe the prevalence and predictive risk factors of colectomy in a large cohort of patients with UC treated with AZA/MP. In a clinical practice this information may help in identifying patients requiring closer surveillance and/or alternative therapeutic interventions.

2. Patients and Methods

2.1. Study Population

The ENEIDA registry (Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales) is a Spanish registry of IBD patients promoted by GETECCU (Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa) that included at the time of this study 13,000 cases of IBD, diagnosed according to the Lennard-Jones criteria.[13] The database is kept under continuous external monitoring for completeness and consistency of the data entered, but only each local investigator can modify the data. This study was approved by the ENEIDA Committee and institutional ethics committee of each participating hospital. Written informed consent was obtained from all patients.

All patients diagnosed between 1980 and 2009 with UC who received AZA/MP treatment for at least 3 months were included. This period was established based on the estimated

Table 1 Demographic data.

	% (n)
Gender (female)	45.6 (608)
Smoking status at diagnosis	
Never or former smoker	81.3 (1084)
Current smoker	18.7 (250)
Colitis extent (Montreal classification)	
E1	4.2 (56)
E2	39.4 (525)
E3	56,5 (753)
EIMs	19.4 (258)
Familial cases	13.2 (176)
Appendectomy rate	4.3 (57)
Decade of diagnose	
1980–1989	9.6% (128)
1990–1999	34.5% (465)
2000–2009	55.5% (741)
Median (IQR)	
Follow-up from diagnosis (months)	98 (53–162)
Time under AZA/MP (months)	37 (15–65)
Age at diagnosis (years)	33 (24–44)
AZA dosage (mg/day)	150 (100–150)
MP dosage (mg/day)	75 (50–100)

EIMs, extraintestinal manifestations; IQR, interquartile range; AZA/MP, azathioprine or mercaptopurine.

lag-time to achieve a full therapeutic effect. Patients who received IMS for other indications (e.g. rheumatologic diseases) were excluded, as well as patients who underwent colectomy due to dysplasia or colorectal cancer.

Parameters recorded for each patient were: age at diagnosis, gender, smoking history, family history of IBD, disease extent according to the Montreal classification,[14] extraintestinal manifestations (EIMs) and therapeutic requirements throughout the course of the disease. EIMs included arthritis, iritis/uveitis, erythema nodosum, pyoderma gangrenosum and aphthous stomatitis. We analyzed the requirements for corticosteroid (CS) treatment ever during the disease and patient response according to the ECCO consensus definitions (steroid-dependence or steroid-refractoriness)[15]; initial and final dates of thiopurine (AZA/MP) treatment, as well as the need for cyclosporine (CsA) or anti-TNFα therapy any time during follow-up and the indication for colectomy (persistent and intractable diseases or acute complication). Combination therapy was defined as receiving AZA/MP and antiTNFα concomitantly at least during two months. We differentiated those patients who were under AZA/MP and antiTNFα concomitantly from the beginning, from those who were under combination therapy during follow-up but one of the drugs was started first.

2.2. Statistical Analysis

Continuous data are expressed as the median and percentiles (interquartile range (IQR) 25–75th percentile). Proportions are expressed as percentages and 95% confidence intervals (95% CI) and they were analyzed by χ^2 test. Follow-up for each patient was based on the date of diagnosis and the date of the last follow-up or surgery.

The cumulative probabilities of colectomy-free survival were estimated using Kaplan–Meier method. Predictors for colectomy were analyzed by univariate analysis using log-rank test. All variables that obtained a *P* value <0.1 were included into a Cox proportional hazard regression using stepwise selection method. Results were reported as hazard ratios (HR) with 95% CI. All *P* values were two-sided and *P*-values less than 0.05 were considered statistically significant.

3. Results

3.1. Baseline Characteristics

A total of 5753 patients with UC diagnosed between 1980 and 2009 had been included in ENEIDA database at the moment of the study. We selected those patients that have been under AZA/MP for at least 3 months. One thousand three-hundred and four patients (22.6%) were included. Demographic characteristics are summarized in Table 1. The median follow-up from diagnosis was 98 months (IQR 53–162 months).

3.2. Colectomy

Of the 1334 patients enrolled, 119 underwent colectomy (8.9%). One-hundred and fourteen colectomies were due to chronic active disease refractory to medical treatment and 5 were due to toxic megacolon or perforation. The median time between UC diagnosis and the date of surgery was 54 months (IQR 27–117) and the median time between AZA/MP initiation and colectomy was 26 months (IQR 12–42). The cumulative probability of colectomy from the diagnosis was 0.4% (95% CI: 0.06–0.74) at 1 year, 5.3% (95% CI: 4.1–6.5) at 5 years, 8.8% (95% CI: 6.9–10.6) at 10 years and 12.7% (95% CI: 9.9–15.5) at 15 years (Fig. 1). The colectomy incidence rate was 9.4 per 1000 UC patient-year.

3.3. Medical Treatment

Thiopurine treatment was started within a median time of 30 months (IQR 8–89) after the UC diagnosis. The median

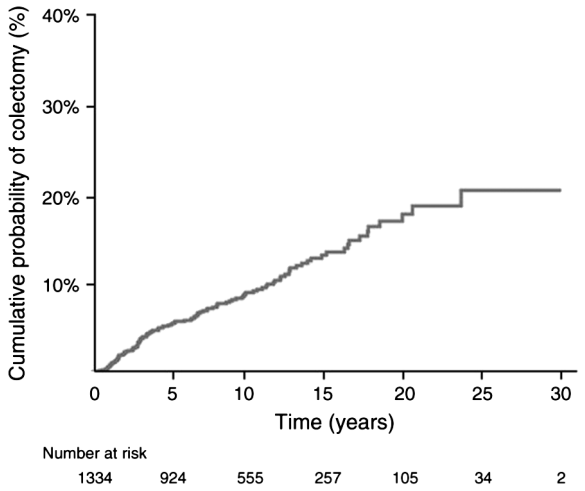

Figure 1 Cumulative probability of colectomy.

Table 2 Colectomy rates and predictors of colectomy: univariate and multivariate analyses.

Covariates	Colectomy rates	Univariate	Multivariate	
	(%)	Log-rank *P* value	HR	95% CI
Gender (male/female)	5.4/3.5	0.09	–	–
Age at diagnosis (younger and older than 35 years)	8.7/9.3	0.2	–	–
Smoking status (current/never or former smoker)		0.09	–	–
Extensive colitis (E1, E2, E3)	0.1/5.7/6.6	<0.0001	1.7	1.1–2.6
EIMs (yes/no)	12.9/7.7	0.08	1.5	1.0–2.4
Familial cases (yes/no)	10.8/8.6	0.45	–	–
Appendectomy (yes/no)	11.1/8.9	0.67	–	–
Cyclosporin (yes/no)	17.7/7.3	<0.0001	2.4	1.6–3.7
AntiTNFα (yes/no)	13.6/7	<0.0001	2.3	1.5–3.4
Combination therapy (from the beginning/during follow-up)	8.8/15.4	0.17	–	–
Time to AZA/MP				
<33 months	11.1	<0.0001	4.9	3.2–7.8
>33 months	6.3	<0.0001	Reference	

EIMs, extraintestinal manifestations; AZA/MP, azathioprine or mercaptopurine; HR, hazard ratio; CI, confidence intervals.

time on AZA/MP was 37 months (IQR 15–69). The median dosage of AZA was 150 mg/day and the median dosage of MP was 75 mg/day. Data about patient weight was not recorded on the ENEIDA registry. One-hundred and eight out of 119 colectomized patients received AZA/MP until colectomy. Only in 11 patients AZA/MP was stopped at least for 6 months before colectomy, in 7 of them because of adverse effects (gastrointestinal intolerance in 5; acute pancreatitis in 1 and leucopenia in 1).

All patients included in the study received corticosteroids (CS) prior to thiopurines. Regarding the previous CS response, thiopurines were indicated in 70.2% of patients for steroid-dependency and in 29.8% for steroid-refractoriness. Two-hundred and three (15.2%) patients received cyclosporine (CsA): 94% of them for induction prior to AZA/MP for maintenance of remission and 6% received CsA while they were under AZA. The median time between CsA initiation and colectomy was 17 days (IQR 9–32). A total of 391 (29.3%) patients were treated with an antiTNFα drug (95.9% receiving infliximab), after a median time of 46 months (IQR 19–103) after UC diagnosis. The median time between the AZA/MP initiation and the beginning of antiTNFα therapy was 11 months (IQR 1–32). Up to 68 patients (17.4%) received combination therapy (AZA/MP and antiTNFα) from the beginning, 201 patients (51.4%) received combination therapy during follow-up but not both drugs from the beginning and 122 patients (31.2%) received antiTNFα in monotherapy after AZA/MP withdrawal. Colectomy rates were not statistically different between those three groups of patients: 8.8%, 15.4% and 13.1%, $P = 0.68$.

Table 3 Predictors of colectomy adjusted by a decade of diagnosis: univariate and multivariate analyses.

Covariates	1980–1989			1990–1999			2000–2009		
	Univariate	Multivariate		Univariate	Multivariate		Univariate	Multivariate	
	Log-rank *P* value	HR	95% CI	Log-rank *P* value	HR	95% CI	Log-rank *P* value	HR	95% CI
Gender	0.9	–	–	0.7	–	–	0.012	–	–
Age at diagnosis	0.9	–	–	0.95	–	–	0.37	–	–
Smoking status	0.5	–	–	0.47	–	–	0.018	–	–
Colitis extent	0.04	–	–	0.03	–	–	0.007	–	–
EIMs	0.86	–	–	<0.0001	3.0	1.6–5.8	0.85	–	–
Familial cases	0.84	–	–	0.2	–	–	0.84	–	–
Appendectomy	0.45	–	–	0.13	–	–	0.73	–	–
Cyclosporin	0.032	–	–	<0.0001	2.9	1.5–5.7	0.001	2.5	1.4–4.6
AntiTNFα	0.86	–	–	0.081	–	–	<0.0001	3.4	1.9–6.1
Combination therapy	0.37	–	–	0.28	–	–	0.49	–	–
Time to AZA/6MP									
<33 months	0.006	9.7	1.3–75.8	<0.0001	4.6	2.4–8.8	<0.0001	3.5	1.6–8.0
>33 months		Reference			Reference			Reference	

EIMs, extraintestinal manifestations; AZA/MP, azathioprine or mercaptopurine; HR, hazard ratio; CI, confidence intervals.

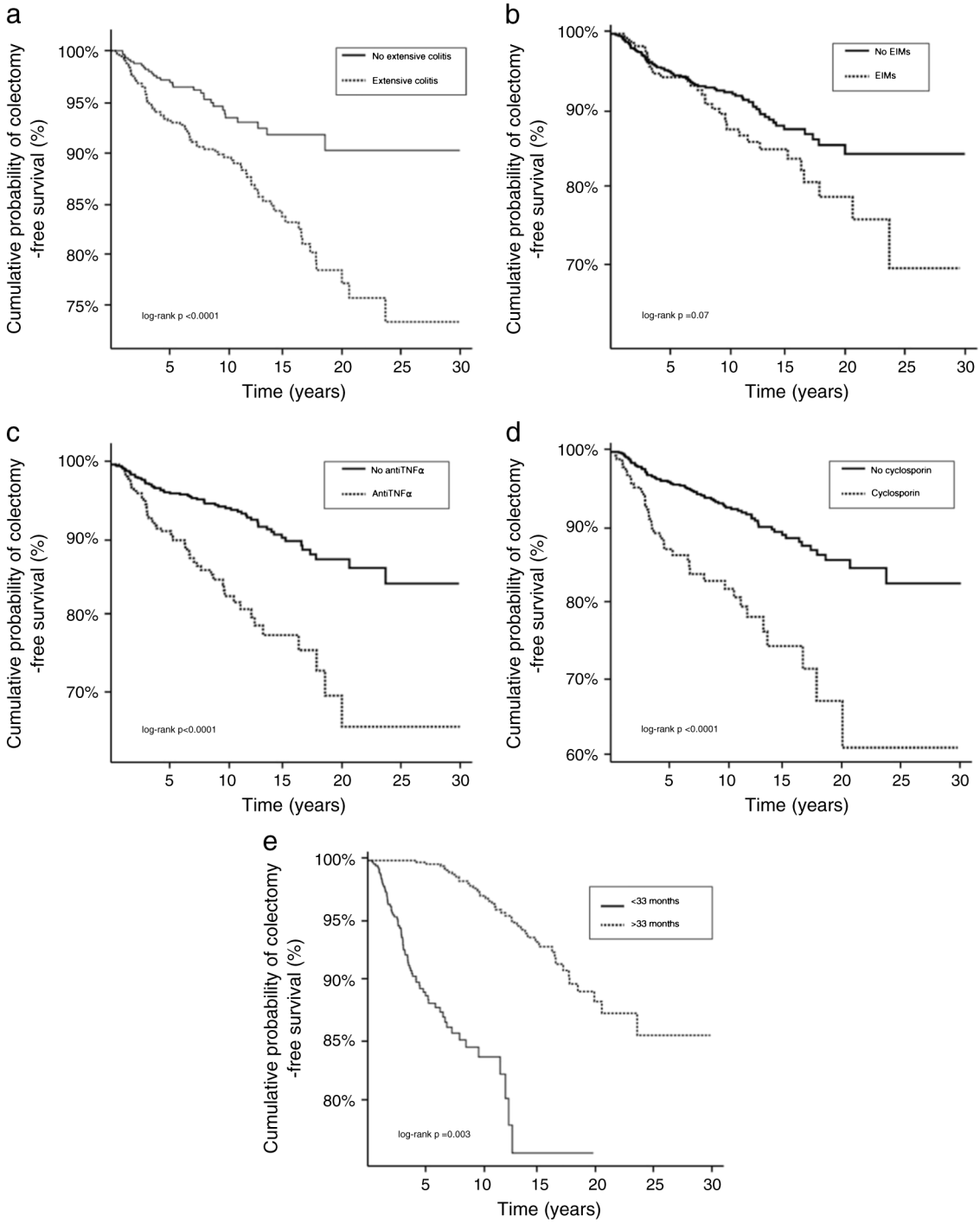

Figure 2 a) Cumulative probability of colectomy-free survival stratified by colitis extent. b) Cumulative probability of colectomy-free survival stratified by extraintestinal manifestations (EIM). c) Cumulative probability of colectomy-free survival stratified by a need for antiTNFα. d) Cumulative probability of colectomy-free survival stratified by a need for cyclosporine (CsA). e) Cumulative probability of colectomy-free survival stratified by time of introduction of thiopurines.

3.4. Predictive Risk Factors of Colectomy

Univariate and multivariate analyses were performed to identify independent predictors of colectomy, adjusted by a decade of diagnosis of UC. Results are summarized in Tables 2 and 3, and Kaplan–Meier curves in Fig. 2. Overall, independent predictors of colectomy were: Extensive colitis (HR 1.7, 95% CI: 1.1–2.6), EIMs (HR 1.5, 95% CI: 1.0–2.4), need for antiTNFα (HR 2.3, 95% CI: 1.5–3.4), and need for CsA (HR 2.4, 95% CI: 1.6–3.7). Likewise the time between diagnosis and initiation of AZA was shown as an independent risk factor for colectomy: introduction of AZA/MP within the first 33 months from the UC diagnosis was

associated to a higher risk of colectomy (HR 4.9, 95% CI: 3.2–7.8), considering receiving AZA/MP after the 33rd month as the reference category (HR 1), and this risk factor appeared in the adjusted analysis by a decade of diagnosis.

4. Discussion

The present study defines the colectomy rates and the risk of colectomy in a large cohort of 1334 UC patients treated with AZA/MP. We observed that 8.9% of patients underwent colectomy in a median time of 2 years after AZA/MP initiation. Disease extent, EIMs, need for antTNFα after initiation of AZA/MP or need for CsA previous to AZA/MP and need for AZA/MP within the first 2.8 years after diagnosis were independent predictors for colectomy.

To our knowledge, the probability of colectomy and the analysis of risk factors for colectomy have not been previously assessed so far in patients under thiopurines. In our large series of patients, we found that cumulative probability of colectomy was quite low: 5.3% at 5 years and 8.8% at 10 years. These values are clearly below the rate recently reported by Targownik et al. of 24.2% at 5 years in the analysis of subgroup patients treated with AZA/MP.[8] This discrepancy may be explained by differences in the methodological design and the small number of patients receiving IMS drugs in the Canadian cohort.

We specifically assessed the risk of colectomy regarding disease characteristics, other therapeutic requirements and the time between diagnosis and AZA/MP initiation. Patients with extensive colitis had a 1.7-fold higher risk of colectomy than those with left-sided colitis or proctitis, which is concordant to previous studies.[7,9,16] EIMs and their association to disease severity and risk of colectomy had been less analyzed in the literature. Only in a French population-based cohort of pediatric UC was a risk of 3.5 times greater found in patients with EIMs than those without EIMs,[17] which is above our findings, although pediatric and adult UC are not comparable.

In our study, nearly a third of patients received antiTNFα and they had 2.5-fold higher risk of colectomy. Data about impact of antiTNFα upon long-term colectomy risk are scarce in real-life setting. One recent study did not find a relationship between the use of antiTNFα and reduction of colectomy rates in a referral center-based cohort.[18] There are several factors that could explain our results that cannot be fully compared to previous studies. First, stratification by AZA/MP treatment represented a selection of more severe patients, in which infliximab was not the first line therapy. Second, infliximab was authorized for moderate to severe UC in Spain since 2006, hence, the longitudinal follow-up is short to rule out the impact of infliximab upon colectomy rates. Nevertheless, the use of antiTNFα remained a predictor of colectomy when adjustment by decade of diagnosis was performed.

The predictive factors found in our series might be considerate as markers of severe disease. Therapeutic benefit of these drugs is probably outweighed by bias selection. We specifically analyzed the role of combination therapy with AZA/MP and antiTNFα, and no differences were found in terms of colectomy rates (8.8% vs 15.4%, P = ns) between both groups. The need for CsA prior to initiation of AZA/MP was also a predictive factor of surgery, concordant with other series.[18]

We found that patients who received AZA/MP within the first 3 years from the disease onset was related to a higher risk of colectomy in the survival analysis and multivariate analysis. Furthermore, it remained as an independent predictor of surgery in the stratified analysis by decade of diagnosis. So far, we did not find any published data regarding the relationship between the time of starting AZA/MP and colectomy.

Previous data support our findings that suggested that first years of the disease are crucial for patient prognosis.[7,16,19] Thus, the need for AZA/MP in the first three years of disease could serve as a red flag to identify patients with an increased risk of colectomy. Recent data about more intensive management with combination therapy showed that it was superior to monotherapy with AZA or antiTNFα in inducing steroid-free remission.[20] Although controlled data about risk of colectomy in patients with combination therapy is lacking, this strategy might be a reasonable alternative for trying to reduce surgery rates in patients at high colectomy risk. Our data do not support this hypothesis; however, there was a trend to diminish colectomy rates in the subgroup of patients with combination therapy from the beginning. We think that statistical significance was not achieved due to the small number of cases and probably due to the shorter follow-up. Long-term follow-up and controlled studies would be necessary in order to confirm that combination therapy is able to reduce surgery rates.

The main limitation of our study was that disease activity and hospitalizations were not recorded in the ENEIDA registry, thus, these parameters had not been considered. In addition, treatment strategies had changed through the years. For this reason we performed a different multivariate analysis by a decade of diagnosis and we selected only patients under thiopurines, trying to diminish the possible time trend bias.

In conclusion, extensive UC, EIMs, need for CsA or anti-TNFα ever and need for AZA/MP treatment within the first three years after diagnosis are associated with a higher risk of colectomy, which is required in nearly one-tenth of patients with UC patients under thiopurines. Those risk factors could help to stratify the risk in further controlled studies in UC.

Conflict of Interest

Elena Ricart has served as a speaker, consultant and advisory member from MSD and Abbvie. Xavier Calvet has served as a speaker, consultant and advisory member and has received research funding from MSD and Abbvie. Javier P Gisbert has served as a speaker, consultant and advisory member and has received research funding from MSD and Abbvie. The other authors declare no potential conflicts of interest.

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Investigators of ENEIDA project:

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Specific author contribution:

ACV, LM and MA: Planning and conducting the study; collecting data and drafting the manuscript. ER, VSG, EGP, MI and AG: Collecting the data. ED, JPG, IMJ, FRM, FG, XC, OM, NVR, ME and MV: Collecting the data and drafting the manuscript.

All authors have approved the final draft submitted.

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