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Comparison between tofacitinib and ustekinumab as a third-line therapy in refractory ulcerative colitis: A multicenter international study

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Abstract

Background: Ustekinumab and tofacitinib have recently been approved for the management of moderate to severe ulcerative colitis (UC). However, there is no evidence on how they should be positioned in the therapeutic algorithm. The aim of this study was to compare tofacitinib and ustekinumab as third-line therapies in UC patients in whom anti-TNF and vedolizumab had failed.

Methods: This was a multicenter retrospective observational study. The primary outcome was disease progression, defined as the need for steroids, therapy escalation, UC-related hospitalization and/or surgery. Secondary outcomes were clinical remission, normalization of C-reactive protein, endoscopic remission, treatment withdrawal, and adverse events.

Results: One-hundred seventeen UC patients were included in the study and followed for a median time of 11.6 months (q_1–q_3, 5.5–18.7). Overall, 65% of patients were treated with tofacitinib and 35% with ustekinumab. In the entire study cohort, 63 patients (54%) had disease progression during the follow-up period. Treatment

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with ustekinumab predicted increased risk of disease progression compared to treatment with tofacitinib in Cox regression analysis (HR: 1.93 [95% CI: 1.06–3.50] $p = 0.030$). Twenty-eight (68%) patients in the ustekinumab group and 35 (46%) in the tofacitinib group had disease progression over the follow-up period (log-rank test, $p < 0.054$). No significant differences were observed for the secondary outcomes. Six and 22 adverse events occurred in the ustekinumab and tofacitinib groups, respectively (15% vs. 31%, $p = 0.11$).

Conclusions: Tofacitinib was more efficacious in reducing disease progression than ustekinumab in this cohort of refractory UC patients. However, prospective head-to-head clinical trials are needed as to confirm these data.

KEYWORDS
biologics, inflammatory bowel disease, tofacitinib

INTRODUCTION

Ulcerative colitis (UC) is a chronic remitting and relapsing inflammatory bowel disease.[1] The current therapeutic algorithm positions monoclonal antibodies and small molecules as valid therapeutic options in patients in whom corticosteroids, 5-aminosalicylates, and immunosuppressants have failed to induce and maintain remission.[2] However, 30% of patients are primary non-responders and 50% become secondary non-responders to any biological agent or small molecule.[3] In addition, there is scarce evidence, and mostly indirect, on which drug should be positioned as a first-, second- or third-line therapy.[4] Anti-tumor necrosis factor (TNF) biosimilars are usually administered as a first-line biological therapy because of their low direct costs and reimbursement policies.[5] Vedolizumab was the first biological approved in UC with a mechanism of action different from TNF blockage and is generally used in patients who would have failed anti-TNF therapy or have contraindications to anti-TNF agents.[6] More recently, tofacitinib and ustekinumab have been approved for the treatment of UC.[7,8] Given their recent approval, it is likely that they will be used in many patients after failing treatment with anti-TNF and vedolizumab. There is scarce evidence on which the drug would be the more beneficial therapeutic option —tofacitinib or ustekinumab— both in the short- and long-term in patients with UC in whom at least two lines of advanced therapy have failed.[9] Therefore, our aim was to compare tofacitinib and ustekinumab as a third-line therapy in UC patients who failed or were intolerant to anti-TNF (at least one) and vedolizumab in order to provide clinicians with data for drug positioning in the therapeutic algorithm of UC patients.

Key summary

Summarize the established knowledge on this subject

- There is no evidence on which drug to choose as third-line in patients with ulcerative colitis who have failed TNF-alpha inhibitors and vedolizumab.

What are the significant and/or new findings of this study?

- Tofacitinib is more efficacious in reducing disease progression than ustekinumab in refractory UC patients.
- This study provides data to define how to position ustekinumab and tofacitinib in the treatment algorithm of patients with moderate-to-severe ulcerative colitis who have failed TNF-alpha inhibitors and vedolizumab.

METHODS

Study design and participants

This was an international multicenter retrospective observational cohort study. Eligible patients had to fulfill the following inclusion criteria: (i) ≥18 years of age at inclusion; (ii) an established diagnosis of UC, defined according to the ECCO standard of care[10]; (iii) documented failure to therapies with anti-TNF (irrespective of the number) and vedolizumab; and (iv) no prior treatment with ustekinumab or tofacitinib. Patients were excluded if they had a diagnosis of unclassified colitis or Crohn's disease or if they were pregnant.

Patients on ustekinumab initially received a single intravenous infusion based on patient's body weight, namely 260 mg (≤55 kg), 390 mg (55–85 kg), or 520 mg (>85 kg), followed by a subcutaneous injection of 90 mg after 8 weeks (induction scheme). Subsequently, they were administered 90 mg of ustekinumab subcutaneously every 8 weeks (maintenance scheme). Tofacitinib was administered orally in a dose of 10 mg *bid* for 8 weeks (induction) followed by 5 mg *bid* (maintenance).

Data collection and management

Data were collected by reviewing the medical notes of patients in the participating centers at treatment initiation (baseline), 3 months, and

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the last follow-up visit. Baseline and follow-up data were collected in a fully anonymized shared case report form (CRF) and included: (i) patient and disease characteristics (age, gender, date of diagnosis, disease phenotype according to the Montreal classification, present and/or past smoking status, presence and type of comorbidities); (ii) history of UC-related medications; (iii) clinical disease activity (assessed by partial Mayo score and patient reported outcomes 2 [PRO2]); (iv) inflammatory bio-markers for disease activity (C-Reactive Protein [CRP]); (v) endoscopic disease activity (Mayo endoscopic score [MES], calculated at baseline and at follow-up endoscopy). (vi) need for steroids or medical therapy escalation (immunosuppressants, re-initiation and/or optimization); (vii) UC outcomes of interest (need for hospitalization, admission to intensive care unit, colorectal dysplasia, colorectal cancer, surgery, discontinuation of ustekinumab/tofacitinib, any infections, serious infections defined as any infections requiring hospitalization, and death), with relevant details on the event.

Study objectives and outcomes

The primary objective of this study was to compare the risk of disease progression over time between the ustekinumab and tofacitinib treatment groups. Disease progression was defined as the occurrence of one or more of the following events: need for steroids, therapy escalation (addition of immunosuppressants, need to increase the dosage of treatment and/or reduce the interval between subsequent administrations or to re-administer an induction dose), hospitalization and/or surgery for any UC-related causes.

Secondary outcomes were (i) clinical remission, defined as normal stool frequency and absence of rectal bleeding (at 12 ± 4 weeks) (ii) normalization of CRP < 5 mg/L (at 12 ± 4 weeks), (iii) endoscopic remission (MES ≤1) at follow-up endoscopy and iv) third-line treatment withdrawal.

Statistical analysis

Descriptive statistics of baseline data are presented as medians and quartiles (q_1–q_3) or as percentages (and 95% confidence intervals [CI]) where appropriate. Differences between treatment groups were tested using the chi-squared or Fisher test for categorical variables and median non-parametric test for continuous variables. Five different outcomes were analyzed: disease progression (primary outcome) and treatment withdrawal on all participants, clinical remission on patients with clinical activity at baseline (n = 72), normalization of CRP on patients with CRP≥ 5 at baseline (N = 56), and endoscopic remission on patients with endoscopy at baseline (N = 62). Differences between treatment groups in clinical remission and normalization of CRP rates at 12 ± 4 weeks were analyzed using χ^2 test and logistic regression. Odds Ratios (ORs) with 95% CI and p- values of the related model parameters were reported. Time-to-event analysis was adopted to analyze differences in disease progression, endoscopic remission and treatment withdrawal, which were collected at varying lengths of follow-up. Time to event was defined as the time from the date of treatment initiation to the date of event or censoring. Kaplan–Meier survival curves were drawn by the treatment group and compared by log-rank test. Cox proportional hazard models were used to analyze treatment differences and the impact of relevant prognostic factors collected at baseline. Hazard ratios (HRs) with 95% CI and p- values of the related model parameters were presented. Univariate and multivariate regression models were applied, with a stepwise approach for the prognostic factors and a fixed treatment term in the multivariate analysis. p values < 0.05 were considered statistically significant. All statistical tests were 2-sided. SaS 9.4 software was used for statistical analyses.

Ethical considerations

The study was performed according to Good Clinical Practice guidelines and was approved by the San Raffaele Hospital Review Board. Data were collected in an anonymized way (Clinical trial number: 24/INT/2022).

The data underlying this article will be shared on reasonable request to the corresponding author.

RESULTS

Population characteristics

One hundred seventeen patients were enrolled from 16 centers across Europe and Israel and were followed for a median time of 11.6 months (q_1–q_3, 5.5–18.7). Patients were predominantly male (58%) with a median age at diagnosis of 30 years (q_1–q_3, 20–49). Overall, 41 patients (35%) received ustekinumab and 76 patients (65%) received tofacitinib (Table 1). At baseline, patients treated with ustekinumab were taking concomitant immunosuppressants in a significantly higher percentage compared to the tofacitinib group (12% vs. 1%, p = 0.010), and a significantly higher percentage of patients treated with tofacitinib was clinically active (median value of PMS, 6 [4–7] vs. 4 [2.5–5], p < 0.001; PMS> 2, 96% vs. 75%, p = 0.001) and had higher CRP median values (12.0 [5.2–19.3] vs. 7.0 [3.2–11.0], p = 0.002). Other baseline factors were similarly distributed between the two treatment groups (Table 1).

Effectiveness of ustekinumab and tofacitinib

Disease progression

Overall, 63 patients (54%) had disease progression over a median time of 7.0 months (q_1–q_3, 3.6–15.8). Treatment with ustekinumab had an increased risk of disease progression compared with

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TABLE 1 Characteristics of patients at inclusion in the study.

	Tofacitinib	Ustekinumab	All	*p*-value
N	76	41	117	
Male, *N* (%)	46 (60.5)	22 (53.7)	68 (58.1)	0.47
Age at diagnosis, years				
Median (q_1–q_3)	30.5 (19.4 – 47.6)	27.3 (22.5 – 51.6)	30.0 (20.4 – 49.2)	0.60
Disease duration, years				
Median (q_1–q_3)	7.2 (3.9 - 12.5)	8.3 (4.6 - 13.3)	7.2 (4.0 - 12.9)	0.51
Extent, *N* (%)				
Left-sided	35 (46.0)	19 (46.3)	54 (46.1)	0.97
Extensive	41 (54.0)	22 (53.7)	63 (53.9)	
Smokers, *N* (%)				
No	64 (85.3)	33 (94.3)	97 (88.2)	0.21
Yes	11 (14.7)	2 (5.7)	13 (11.8)	
EIM[a], *N* (%)				
No	70 (92.1)	34 (82.9)	104 (88.9)	0.13
Yes	6 (7.9)	7 (17.1)	13 (11.1)	
PMS				
Median (q_1–q_3)	6 (4–7)	4 (2.5 - 5)	5 (4 - 7)	**0.0003**
PMS> 2, *N* (%)				
No	3 (4.0)	10 (25.0)	13 (11.2)	**0.0012**
Yes	73 (96.0)	30 (75.0)	103 (88.8)	
CRP mg/L				
Median (q_1–q_3)	12.0 (5.2 - 19.3)	7.0 (3.2 - 0.0)	9.9 (4.5 - 18.0)	**0.0029**
CRP ≥5, *N* (%)				
No	15 (19.7)	13 (31.7)	28 (23.9)	0.16
Yes	56 (73.7)	26 (63.4)	82 (70.1)	
MES				
Median (q_1–q_3)	3.0 (2.0 - 3.0)	2.5 (2.0 - 3.0)	3.0 (2.0 - 3.0)	0.14
MES> 1, *N* (%)				
No	3 (4.4)	5 (13.9)	8 (7.6)	0.12
Yes	66 (95.6)	31 (86.1)	97 (92.4)	
Ulcers (MES> 2), *N* (%)				
No	26 (37.7)	18 (50.0)	44 (41.9)	0.22
Yes	43 (62.3)	18 (50.0)	61 (58.1)	
PRO2> 0, *N* (%)				
No	2 (2.6)	3 (7.5)	5 (4.3)	0.34
Yes	74 (97.4)	37 (92.5)	111 (95.7)	
Steroids, *N* (%)				
No	61 (80.3)	30 (73.2)	91 (77.8)	0.38
Yes	15 (19.7)	11 (26.8)	26 (22.2)	

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TABLE 1 (Continued)

	Tofacitinib	Ustekinumab	All	*p*-value
IMS[b], *N* (%)				
No	75 (98.7)	36 (87.8)	111 (94.9)	**0.010**
Yes	1 (1.3)	5 (12.2)	6 (5.1)	
Failure to 1 or >1 anti-TNF, *N* (%)				
1	66 (86.8)	36 (87.8)	102 (87.2)	0.88
>1	10 (13.2)	5 (12.2)	15 (12.8)	

Note: Values in bold are the significant *p*.

Abbreviations: CRP, C-reactive protein; EIM, extra-intestinal manifestations; IMS, immunosuppressants; MES, Mayo endoscopic subscore; PMS, partial Mayo score; PRO, Patient report outcomes.

[a]4 patients with concomitant ankylosing spondylitis, 1 psoriatic arthritis, 3 psoriases, 1 primary sclerosing cholangitis, 4 peripheral arthritis.

[b]4 patients taking concomitant azathioprine, 1 methotrexate, 1 prograf (heart transplantation).

TABLE 2 Hazard risk (HR) of disease progression in relation to baseline characteristics and treatment.

	Univariate cox PH model		Multivariate cox PH model	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Ustekinumab versus tofacitinib	1.84 (1.04 3.27)	**0.0365**	1.93 (1.06–3.51)	**0.0304**
Sex (female vs. male)	0.83 (0.47 1.50)	0.55		
Age at diagnosis (years)	0.99 (0.97 1.00)	0.14		
Smokers (yes vs. no)	0.72 (0.28 1.82)	0.48		
Disease_duration (years)	0.98 (0.94 1.02)	0.28		
PMS	1.06 (0.92 1.22)	0.42		
PMS> 2 (yes vs. no)	0.96 (0.34 2.67)	0.93		
CRP mg/L	1.02 (1.00 1.04)	**0.014**	1.03 (1.01–1.04)	**0.0012**
CRP≥ 5 (yes vs. no)	1.40 (0.68 2.89)	0.36		
MES	1.54 (0.97 2.45)	0.07		
MES> 1 (yes vs. no)	3.27 (0.79 13.54)	0.10		
Ulcers (yes vs. no)	1.53 (0.86 2.72)	0.15		
PRO2> 0 (yes vs. no)	0.63 (0.86 4.62)	0.65		
Extent extensive (yes vs. no)	1.70 (0.95 3.05)	0.07		
Failure to > 1 anti-TNF (yes vs. no)	0.66 (0.28 1.58)	0.35		
Concomitant steroids (yes vs. no)	2.20 (1.18 4.10)	**0.0136**	2.15 (1.13–4.11)	**0.0202**
EIM (yes vs. no)	0.72 (0.26 2.02)	0.54		

Note: Results of time-to-event analysis (117 patients). Estimates for univariate models are not reported when the model didn't converge. Values in bold are the significant *p*.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; EIM, extra-intestinal manifestations; HR, Hazard Ratio; IMS, immunosuppressants; MES, Mayo endoscopic subscore; PH, Proportional Hazards; PMS, partial Mayo score; PRO, Patient report outcomes.

treatment with tofacitinib in Cox regression analysis (HR: 1.93 [95% CI: 1.06–3.51], $p = 0.030$) (Table 2 and Supplementary Table S5). Twenty-eight (68%) patients in the ustekinumab group and 35 (46%) in tofacitinib group had disease progression over the follow-up period (log-rank test, $p < 0.054$) (Figure 1).

Clinical remission

Seventy-two patients were clinically active at baseline, had a clinical activity reassessment at week 12 ± 4, and were therefore considered for statistical analysis. Fifteen patients (21%) achieved clinical remission; 2/18 (11%) on ustekinumab and 13/54 (24%) on tofacitinib ($p = 0.32$). No significant difference in ustekinumb versus tofacitinib was observed in multivariate logistic regression analysis (OR 0.83 [95% CI 0.14–4.78], $p = 0.84$) (Supplementary Table S1).

Normalization of C-reactive protein

Fifty-six patients had CRP values ≥ 5 mg/L at baseline, had a blood test reassessment at week 12 ± 4 and were therefore considered for

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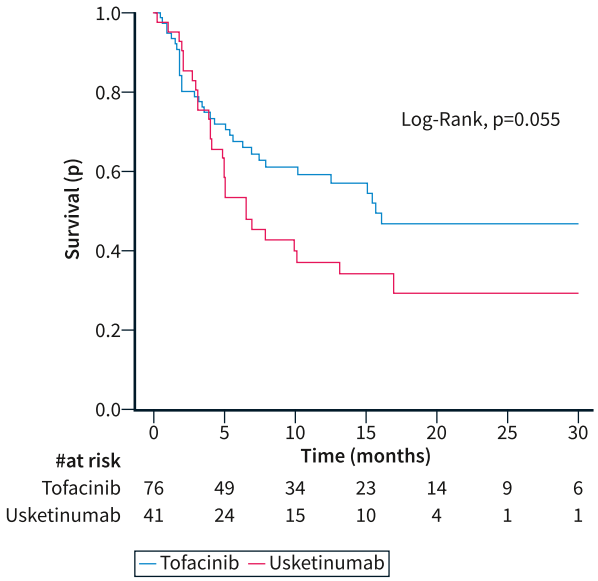

	Tofacitinib	Ustekinumab	All
Disease progression, N (%), No	41 (54.0)	13 (31.7)	54 (46.2)
Disease progression, N (%), Yes	35 (46.0)	28 (68.3)	63 (53.8)
Median (Q_1-Q_3) survival time, months	7.7 (3.6-16.0)	5.9 (4.0-14.9)	7.0 (3.6-15.8)

Disease progression: the need to introduce steroids, therapy escalation, hospitalization and/or surgery for UC-related causes

FIGURE 1 Kaplan–Meier curves for the cumulative probability of disease progression overtime in patients with ulcerative colitis treated with ustekinumab or tofacitinib.

statistical analysis. Twenty-two patients (39%) achieved normalization of CRP (CRP< 5 mg/L); 6/14 (43%) on ustekinumab group and 16/42 patients (38%) on tofacitinib group ($p = 0.75$). No significant difference in ustekinumab versus tofacitinib was observed in multivariate logistic regression analysis (OR 2.99 [95% CI 0.44–20.18], $p = 0.26$) (Supplementary Table S2).

Endoscopic remission

Sixty-two patients with MES≥ 2 at baseline and with endoscopic reassessment during the follow-up period were considered for statistical analysis. Twenty patients (32%) achieved endoscopic remission (MES ≤1) over a median time of 6.3 months (q_1–q_3, 4.1–12.0). In the multivariate Cox regression analysis, no statistically significant difference was observed between ustekinumab and tofacitinib (HR 0.53 [95% CI 0.11–2.45], $p = 0.42$) (Supplementary Table S3). Three out of 19 patients (16%) being administered ustekinumab and 17/43 patients (40%) receiving tofacitinib achieved endoscopic remission (log-rank test, $p = 0.20$).

Treatment withdrawal

Forty patients (34%) discontinued treatment over a median time 11.6 months (q_1-q_3, 5.5–18.7). In the multivariate Cox regression analysis, no statistically significant difference was observed between ustekinumab and tofacitinib (HR 1.89 [95% CI 0.93–3.86], $p = 0.080$) (Supplementary Table S4). Eighteen out of 41 patients (44%) being administered ustekinumab and 22/76 patients (29%) receiving tofacitinib discontinued treatment over time (log-rank test, $p = 0.18$).

Safety of ustekinumab and tofacitinib

Twenty-eight adverse events occurred, 6 in the ustekinumab group and twenty-two in the tofacitinib group (15% vs. 31%, $p = 0.11$).

Patients being administered ustekinumab developed infections due to SARS-CoV-2 ($n = 2$), Clostridioides difficile ($n = 1$), herpes simplex virus ($n = 1$), and symptomatic varicella zoster reactivation ($n = 1$). In the other group of patients having tofacitinib, infections occurred due to SARS-CoV-2 ($n = 13$), Clostridioides difficile ($n = 2$), upper respiratory tract infections ($n = 2$), and lower respiratory tract infections ($n = 1$). No serious infections occurred. Two patients in the tofacitinib group developed hyperlipidemia that required the administration of statins. Two patients developed a colorectal cancer in each of the two treatment groups. Finally, a patient in the tofacitinib group developed a central retinal vein occlusion that necessitated the withdrawal of the drug. The patient was a 45-year-old nonsmoking woman with no risk factors for thromboembolic disease.

DISCUSSION

The management of refractory patients with UC remains a challenge. Head-to-head comparisons of available drugs in a real-life setting are needed to provide more precise indications on how to appropriately position therapies in the treatment algorithm.

This study demonstrated that tofacitinib is more efficacious than ustekinumab as third-line therapy in a cohort of highly refractory UC patients, in terms of reducing the risk of disease progression (USK; HR: 1.93 [95% CI: 1.06–3.50], $p = 0.030$). Though not statistically significant ($p = 0.20$), endoscopic remission occurred only in 16% of patients being administered ustekinumab versus 40% of those having tofacitinib. Similarly, no statistically significant differences were observed for the other secondary outcomes, including clinical remission, normalization of CRP, and treatment withdrawal. Particularly, in line with a previous monocentric study, ustekinumab and tofacitinib were equally effective in inducing clinical remission at week 12±4.[9]

In terms of adverse events, though these were more common in the tofacitinib group than the ustekinumab group (31% vs. 15%), this was not statistically significant ($p = 0.11$). Noteworthy, a central

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retinal vein occlusion occurred in the tofacitinib group, that led to the withdrawal of the treatment. Our data are in line with the long-term safety data of tofacitinib in UC, showing no increased risk of thromboembolic and cardiovascular events.[11] No increased risk of Herpes Zoster reactivation or dyslipidemia was identified, confirming the acceptable safety profile of tofacitinib. Positioning of tofacitinib and ustekinumab in the treatment algorithm of moderate to severe UC should take into account several factors, including the administration route, patient preference and compliance, and rapidity of action. Importantly, data from the ORAL surveillance trial showed that patients with rheumatoid arthritis treated with tofacitinib have an increased risk of cardiovascular events and malignancy.[12] Based on this evidence, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has provided recommendations on the use of JAK inhibitors in UC, limiting their use based on the presence of risk factors (age>65 years, smoking status, increased risk of thrombosis, cardiovascular events or cancer history). Specifically, patients without risk factors should be treated with JAK inhibitors as the next line therapy after failure of anti-TNF agents. On the contrary, in subjects with risk factors, JAK inhibitors should be considered after the failure of anti-TNF agents, vedolizumab or ustekinumab. Head-to-head trials are needed to define how to appropriately position the available drugs in the treatment algorithm in patients without risk factors.[13]

This study has certain limitations, mainly related to the modest sample size and to its retrospective nature, that is, the lack of random allocation in the two drug groups, the lack of previous similar studies to calculate the needed sample size, and the limited follow-up due to the short time from the approval of both medications in the countries of the participating centers. In addition, we were unable to include fecal calprotectin values in the analysis because of missing values in many patients. In line with these limitations, the results coming from an observational study could be influenced by potential confounding factors. To overcome that, we included measured baseline characteristics as confounding in the analysis. We also tried to implement propensity score techniques to obtain a matched sample, but we could not achieve an optimal balance for all confounding factors between treatment groups. On the other hand, this is the first multicenter study comparing both drugs as a third-line therapy in a real-world setting, and despite the small sample size, it provides interesting information about the effectiveness of ustekinumab and tofacitinib after failure of anti-TNF and vedolizumab.

To conclude, tofacitinib seems to be more efficacious in reducing disease progression compared to ustekinumab as a third-line therapy in patients with refractory UC; however, larger prospective head-to-head studies are warranted to improve drug positioning.

AUTHOR CONTRIBUTIONS

All persons who meet the authorship criteria are listed as authors. Mariangela Allocca designed the study and contributed to the literature search and data collection. Gaia Catalano contributed to the literature search and data collection and drafted the manuscript. Edoardo V. Savarino contributed to data collection. María Chaparro contributed to data collection. Asaf Levartovsky contributed to data collection. George Michalopoulos contributed to data collection. Nikos Viazis contributed to data collection. Fotis S. Fousekis contributed to data collection. Andreas Psistakis contributed to data collection. Daniele Noviello contributed to data collection. Catarina Neto do Nascimento contributed to data collection. Benedicte Caron contributed to data collection. Vassiliki Kitsou contributed to data collection. Giorgos Bamias contributed to data collection. María José García contributed to data collection. Eirini Zacharopoulou contributed to data collection. Kalliopi Foteinogiannopoulou contributed to data collection. Ferdinando D'Amico contributed to data collection. Ioannis Koutroubakis contributed to data collection. Pierre Ellul contributed to data collection. Maria Tzouvala contributed to data collection. Laurent Peyrin-Biroulet contributed to data collection. Joana Torres contributed to data collection. Flavio Caprioli contributed to data collection. Konstantinos Karmiris contributed to data collection Angeliki Theodoropoulou contributed to data collection. Konstantinos H. Katsanos contributed to data collection. Dimitrios K. Christodoulou contributed to data collection. Gerassimos J. Mantzaris contributed to data collection. Uri Kopylov contributed to data collection. Javier P. Gisbert contributed to data collection. Silvio Danese contributed to data collection. Fernando Magro contributed to data collection. Gionata Fiorino contributed literature search. Fornari Carla performed data analysis. All authors contributed to the design and critical review of the manuscript, and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Allocca M received consulting fees from Nikkiso Europe, Mundipharma, Janssen, Abbvie, Ferring, Galapagos and Pfizer; Peyrin-Biroulet L reported personal fees from Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, and Samsung Biosepsis; Ellul P received consulting fees from Janssen; Fiorino G received consultancy fees from Ferring, AbbVie, Takeda, Janssen, Amgen, Sandoz, Celltrion, Galapagos; D'Amico F has served as a speaker for Janssen, Galapagos, Sandoz, and Omega Pharma; he has also served as advisory board member for Abbvie, Galapagos, and Nestlè; Danese S served as a speaker, consultant and advisory board member for Schering-Plough, Abbott (AbbVie) Laboratories, Merck, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alfa Wasserman, Genentech, Grunenthal, Pfizer, AstraZeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor and Johnson and Johnson; Gisbert JP has served as speaker, consultant, and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene/Bristol Myers, Gilead/Galapagos, Lilly, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Norgine and Vifor Pharma; Konstantinos Karmiris has served as speaker, consultant and advisory board member for Abbvie, Amgen, Ferring, Galenica, Genesis, Janssen, MSD, Pfizer, Takeda and Vianex; María Chaparro: Speaker, consultant or research or education funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Biogen, Gilead and Lilly; All the other authors did not have any conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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