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Alimentary Tract

Treatment patterns and intensification within 5 year of follow-up of the first-line anti-TNFα used for the treatment of IBD: Results from the VERNE study

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ABSTRACT

Background: Anti-TNFα represent one of the main treatment approaches for the management of inflammatory bowel diseases (IBD). Therefore,the evaluation of their treatment patterns over time provides valuable insights about the clinical value of therapies and associated costs.

Aims: To assess the treatment patterns with the first anti-TNFα in IBD.

Methods: Retrospective, observational study.

Results: 310 IBD patients were analyzed along a 5-year follow-up period. 56.2% of Crohn's disease (CD) patients started with adalimumab (ADA), while 43.8% started with infliximab (IFX). 12.9% of ulcerative colitis (UC) patients initiated with ADA, while 87.1% initiated with IFX. Treatment intensification was required in 28.9% of CD and 37.1% of UC patients. Median time to treatment intensification was shorter in UC than in CD (5.3 vs. 14.3 months; $p = 0.028$). Treatment discontinuation due to reasons other than remission were observed in 40.7% of CD and 40.5% of UC patients, although, in UC patients there was a trend to lower discontinuation rates with IFX (36.6%) than with ADA (66.7%). Loss of response accounted for approximately one-third of discontinuations, in both CD and UC.

Conclusions: Around one-third of IBD biologic-naive patients treated with an anti-TNFα required treatment intensification (earlier in UC) and around 40% discontinued the anti-TNFα due to inappropriate disease control.

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1. Introduction

Inflammatory bowel disease (IBD) comprises two different conditions, Crohn's disease (CD) and ulcerative colitis (UC), characterized by chronic and relapsing inflammation of the gastrointestinal tract. They are disorders produced by a dysregulated immune response against the commensal microbiota, probably as a result of complex interactions among host genetics, immune dysregulation, microbiota behavior and environmental predisposing factors. Associated symptoms, mainly abdominal pain, diarrhea, rectal bleeding, fatigue and anemia, produce a profound impact on patients' quality of life, and prolonged inflammation results in damage to the gastrointestinal tract, sometimes leading to severe disability and complications [1–5].

Anti-tumor necrosis factor-alpha (anti-TNFα) therapies, such as the monoclonal antibodies infliximab (IFX) and adalimumab (ADA), have revolutionized the treatment of IBD. They are effective not only at inducing and maintaining clinical remission and mucosal healing but also in improving patients' quality of life and reducing surgery and hospitalization rates [6]. Hence, anti-TNFα therapies represent one of the main treatment approaches for the management of IBD [7–10]. Unfortunately, up to 40% of IBD patients do not respond to induction therapy (primary nonresponse [PNR]), and between 24% and 46% of successfully treated patients lose control over time (loss of response [LOR]) [11,12]. As a consequence, new therapeutic options have been developed and are available to patients.

The study of treatment patterns over time is becoming increasingly important, as these may provide valuable insights to clinicians and administrators about the real-world utility of therapies and their economic costs; therefore, knowledge regarding treatment patterns may be helpful to inform the selection of the most appropriate therapy in a context where the appropriate choice is often far from obvious.

Although different real-world studies have comparatively assessed the treatment patterns of various anti-TNFα therapies in IBD patients [13–18], only a few of them have been conducted over a longer period of time. These few studies [13,17] are based on analyses of health insurance claims databases, which means that the data sources used are not clinical but administrative, with the well-known limitations of such claims data (poor disease characterization, a lack of data on the clinical reasons leading to medication changes, the impossibility of registering doses and dose adjustments, the need to use arbitrary definitions to draw conclusions on persistent gaps in treatment, or data quality strongly dependent on the accuracy of administrative coding tasks).

As CD and UC are chronic, lifelong conditions, it is essential to characterize treatment patterns across extended time spans and, ideally, using clinical data sources to circumvent the limitations associated with health insurance claims databases.

The objectives of this study were to describe long-term treatment patterns with the first anti-TNFα in a cohort of biologic-naive IBD patients, and to describe the need for treatment intensification and discontinuation rates.

2. Methods

2.1. Study population

VERNE was a retrospective (using hospital patient charts as the source of data), observational, multicenter study involving 24 tertiary hospitals in Spain (ClinicalTrials.gov Identifier: NCT02861118).

The study consecutively included adult patients diagnosed with UC or CD who started their first biologic treatment with an anti-TNFα between June 2011 and June 2013. All patients were prescribed anti-TNFα treatment according to standard clinical practice [19] and gave their written informed consent for study participation. Patients were excluded if they were participating in a clinical trial during the study reference period or if, according to investigator's criteria, were not able to understand and fill in the study questionnaires or to give written informed consent.

The study was reviewed and approved by the corresponding ethics committees. The results obtained in the VERNE study on the impact of both comorbidities and extraintestinal manifestations (EIMs) on the response to anti-TNFα therapy have been published elsewhere [20].

2.2. Patients description

Demographic characteristics (age, gender, ethnicity), smoking habit, and clinical variables (type of IBD, previous treatments, disease location, disease behavior and extraintestinal manifestations) were recorded.

2.3. Clinical outcome evaluation

The following treatment-related parameters were recorded and analyzed: 1) time to treatment with the first anti-TNFα; 2) the frequency of use of different anti-TNFα treatments; 3) rates of anti-TNFα therapy intensification, time to anti-TNFα therapy intensification (defined as the time elapsed from initial treatment date until drug intensification date), and the type of anti-TNFα therapy intensification strategy (dose increase or dosing interval shortening); 4) rates of anti-TNFα therapy discontinuation, time to anti-TNFα therapy discontinuation (defined as the time elapsed from initial treatment date until drug discontinuation date), and reasons for discontinuation (remission, PNR, LOR, partial response (PR), side effects (SEs), other); 5) treatments received for IBD after the discontinuation of the first biologic; and 6) concomitant treatments for IBD received during induction and maintenance of biologic therapy.

2.4. Statistical analysis

Baseline parameters were analyzed descriptively, calculating medians and interquartile ranges (IQRs) for continuous variables and percentages for categorical variables. Kaplan-Meier survival analyses were used to estimate times to treatment intensification and to treatment discontinuation, and a log-rank test was applied to compare survival curves. $P < 0.05$ was considered the level of significance. All data analyses were performed using IBM SPSS Statistics 22.0 Statistical Package for Windows.

3. Results

3.1. Patient characteristics and follow-up times

Initially, 357 patients were identified for inclusion, but 47 of them were eventually excluded from the analysis (screening failures), resulting in a total of 310 analyzed patients, 194 diagnosed with CD and 116 with UC. The clinical and demographic characteristics of the patients are shown in Table 1. The median (IQR) follow-up times after treatment administration were 59.8 (53.2, 65.8) and 59.8 (53.4, 65.1) months for CD and UC, respectively.

3.2. Frequency of use and time to treatment initiation of first anti-TNFα treatment

The median (IQR) times from the diagnosis of IBD to treatment with the first anti-TNFα were 45.5 (11.6, 156.0) and 43.8 (10.8, 143.8) months for CD and UC, respectively.

Table 1
Subjects' clinical characteristics and demographics.

		CD		UC		Total	
		N	%	N	%	N	%
Sex	Male	103	53.1	63	54.3	166	53.5
	Female	90	46.4	47	40.5	137	44.2
	Not available	1	0.5	6	5.2	7	2.3
	Total	194	100.0	116	100.0	310	100.0
Age, median (IQR)		194	43.0 (34.0-51.5)	116	46.0 (38.0-57.8)	310	44.0 (36.0-53.5)
Ethnicity	Caucasian	189	97.4	108	93.1	297	95.8
	Other	5	2.6	8	6.9	13	4.2
	Total	194	100.0	116	100.0	310	100.0
Smoking habits	Nonsmoker	86	44.3	70	60.3	156	50.3
	Ex-smoker	52	26.8	37	31.9	89	28.7
	Smoker	55	28.4	7	6.0	62	20.0
	Not available	1	0.5	2	1.7	3	1.0
	Total	194	100.0	116	100.0	310	100.0
Previous treatments for IBD[†]	Aminosalicylates	105	54.1	106	91.4	211	68.1
	Corticosteroids	148	76.3	105	90.5	253	81.6
	Immunosuppressants	159	82	84	72.4	243	78.4
	Antibiotics	79	40.7	27	23.3	106	34.2
Other previous treatments	Pain medications	53	27.3	28	24.1	81	26.1
	Antidiarrheals	14	7.2	9	7.8	23	7.4
	Antidepressants	11	5.7	13	11.2	24	7.7
Location of disease	L1= Terminal ileum	72	37.3			72	23.6
	L2= Colon	30	15.5	9	8.0	30	9.8
	L3= Ileum and colon	86	44.6	49	43.8	86	28.2
	L4= Upper GI track	5	2.6	54	48.2	5	1.6
	E1= Proctitis	193[*]	100.0	112[*]	100.0	9	3.0
	E2= Left colitis					49	16.1
	E3= Extensive colitis					54	17.7
	Total					305	100.0
Disease behavior	B1= Inflammatory	86	44.6				
	B2= Stenosis	40	20.7				
	B3= Fistulizing	34	17.6				
	(B1p+B2p+B3p) = perianal	33	17.1				
	Total	193[*]	100.0				
Extraintestinal manifestations	Yes	51	26.3	38	32.8	89	28.7
	Total	194	100.0	116	100.0	310	100.0

[†] Patients could have taken more than one previous medication.
[*] Not available: 1 patient (CD); 4 patients (UC).

Table 2
Biologic treatment intensification during follow-up: Regimens and time to intensification.

		IBD					
		Crohnś disease		Ulcerative colitis		Total	
		N	%	N	%	N	%
Patients under biologic treatment intensification		56	28.9	43	37.1	99	31.9
Total IBD patients		194		116		310	100.0
Regimens	Dose increase	11	19.6	13	30.2	24	24.2
	Interval shortening	22	39.3	10	23.3	32	32.3
	Both regimens	23	41.1	20	46.5	43	43.4

[*]One patient with missing treatment intensification date.
IQR: Interquartile range.

One hundred nine CD patients (56.2%) started anti-TNF treatment with ADA, while 85 (43.8%) started with IFX. In patients with UC, 15 (12.9%) initiated anti-TNFα therapy with ADA, while 101 were initially treated with IFX (87.1%).

3.3. Anti-TNFα therapy intensification

Fifty-six CD patients (28.9%) and 43 UC patients (37.1%) required anti-TNFα treatment intensification, with similar proportions of patients on ADA and IFX, respectively (29.4% and 28.2% in the CD subgroup, and 33.3% and 37.6% in the UC subgroup). Strategies implemented for treatment intensification are displayed in Table 2. The most common intensification strategy, used in more than 40% of patients with CD and UC who needed it, was a combination of dose increase and a dosing interval shortening of the respective anti-TNFs. The median time to intensification was 14.3 months for CD patients and 5.3 months for UC patients (log-rank test, $p = 0.028$; Fig. 1a).

Regardless of the type of IBD diagnosis, CD or UC, the time to treatment intensification did not significantly differ between patients receiving ADA and those receiving IFX (Figs. 1b and 1c). However, in UC patients, there was a trend toward a shorter median time to intensification with ADA than with IFX (2.4 vs. 6.3 months).

3.4. Anti-TNFα therapy discontinuation

Ninety-two CD patients (47.4%) and 65 UC patients (56.0%) discontinued anti-TNFα treatment during the follow-up. Discontinuation due to reasons other than remission was observed in 79 CD patients (40.7%) and 47 UC patients (40.5%).

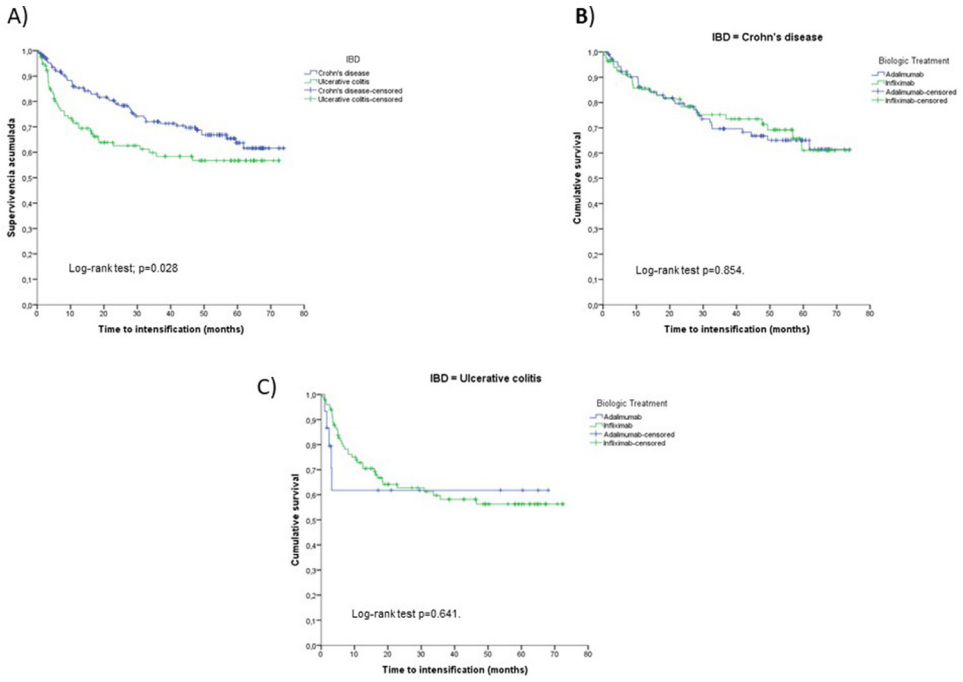

Fig. 1. A) Time to intensification (months) by the type of IBD; B) CD patients: Time to intensification (months) by anti-TNF treatment; C) UC patients: Time to intensification (months) by anti-TNF treatment

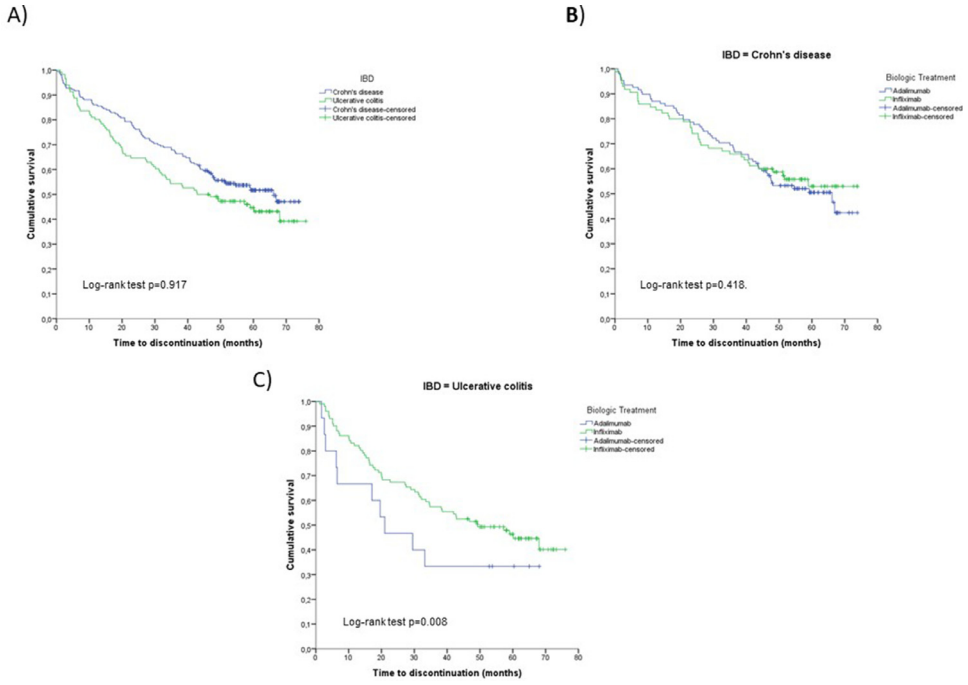

Fig. 2. A) Time to discontinuation (months) due to reasons other than remission by IBD type; B) CD patients: Time to discontinuation (months) due to reasons other than remission by anti-TNF treatment; C) UC patients: Time to discontinuation (months) due to reasons other than remission by anti-TNF treatment

The survival curves assessing time to discontinuation due to reasons other than remission did not show significant differences between CD patients and UC patients (log-rank test $p = 0.917$; Fig. 2a). However, discontinuation rates seemed to differ within the UC subpopulation between IFX-treated patients (36.6%) and ADA-treated patients (66.7%).

No differences were observed in the proportion of patients who discontinued IFX in the CD and UC subpopulations (37%). On the contrary, 67% of CD patients and 44% of UC patients discontinued ADA. Within the CD population, no significant differences in time to discontinuation were observed between patients receiving IFX and those receiving ADA (Fig. 2b). Conversely, in UC patients, the survival analyses showed a significantly longer time to treatment discontinuation with IFX than with ADA (log-rank test $p = 0.008$; Fig. 2c). Among UC patients who discontinued treatment, the median time to discontinuation was 15.3 months for those receiving IFX and 11.8 months for those receiving ADA, while for CD patients who discontinued treatment, median times to drug discontinuation were 23.0 months and 27.4 months for IFX and ADA, respectively.

Table 3
Biologic treatment discontinuation during follow-up due to reasons other than remission.

		Crohnś disease		IBD Ulcerative colitis		Total	
		N	%	N	%	N	%
Biologic treatment discontinution	Due to causes other than remission	79	40.7%	47	40.5%	126	40.6%
	Total	194	100.0%	116	100.0%	310	100.0%
Discontinuation treatment reason*	PNR	9	11.4%	9	19.1%	18	14.3%
	LOR	26	32.9%	18	38.3%	44	34.9%
	PR	6	7.6%	2	4.3%	8	6.3%
	SEs	18	22.8%	10	21.3%	28	22.2%
	Other reasons	20	25.3%	8	17.0%	28	22.3%
	Total	79	100.0%	47	100.0%	126	100.0%

PNR: Primary nonresponse; LOR: Loss of response; PR: Partial response; SE: Side effects.
* Percentages calculated over patients with treatment discontinuation.

Table 4
Concomitant treatments during induction and maintenance phases*,$

		Crohnś disease		IBD Ulcerative colitisN		Total	
		N	%	N	%	N	%
Induction phase	Corticosteroids	54	27.8	65	56.0	119	38.4
	Immunosuppressants	121	62.4	65	56.0	186	60.0
	Total	194	100.0	116	100.0	310	100.0
Maintenance phase	Corticosteroids	58	29.9	45	39.1	103	33.3
	Immunosuppressants	131	67.5	70	60.9	201	65.0
	Total	194	100.0	115*	100.0	309	100.0

* One UC patient with missing concomitant information during the maintenance phase.
$ Treatments were not continuously administered during the study follow-up period.

3.4.1. Discontinuations due to PNR

Overall, 5.8% of patients discontinued the anti-TNFα due to PNR (4.6% of CD patients and 7.8% of UC patients). PNR accounted for 14.3% of the discontinuations due to reasons other than remission (11.4% in CD patients and 19.1% in UC patients) (Table 3).

3.4.2. Discontinuations due to LOR

LOR was the most common reason for treatment discontinuation. Overall, 14.2% of patients discontinued the anti-TNFα due to LOR (13.4% of CD patients and 15.5% of UC patients). LOR accounted for 34.9% of the discontinuations due to reasons other than remission (32.9% in CD patients and 38.3% in UC patients) (Table 3).

3.4.3. Discontinuations due to safety reasons

Side effects led to anti-TNFα discontinuation in 9.0% of patients (9.3% of CD patients and 8.6% of UC patients), They were the reason for 22.2% of the discontinuations due to reasons other than remission (22.8% in CD patients and 21.3% in UC patients) (Table 3).

Overall, almost 50% of the patients discontinued the anti-TNFα treatment because of LOR or PNR (Table 3).

3.5. Concomitant treatments during the induction and maintenance phases

Concomitant treatments, defined as those medications administered at any time during follow-up, based on specific patient requirements, are summarized in Table 4. A high proportion of IBD subjects were concomitantly treated with immunosuppressants at both the induction phase (60.0%) and at any time along the maintenance phase (65.0%), with similar proportions for CD and UC patients. Conversely, corticosteroids were more frequently administered to UC patients both during the induction phase (CD 27.8% vs UC 56.0%) as well as at any time during the maintenance phase (CD 29.9% vs UC 39.1%).

3.6. Treatments for IBD after the discontinuation of the first anti-TNFα

Among patients who discontinued the first anti-TNFα treatment due to reasons other than remission, 76.2% received a second biologic therapy after the discontinuation of the first biologic treatment (72.2% in CD and 83.0% in UC). The second biologic was another anti-TNFα in 89.6% of patients (87.8% in CD and 92.3% in UC) and vedolizumab in 9.4% of patients (10.5% in CD and 9.0% in UC). Ustekinumab was the second biologic agent in 1.7% of patients with CD.

4. Discussion

To the best of our knowledge this is the first long-term retrospective medical-record based study assessing the association between the comorbidity profile in patients with IBD and PNR or LOR to anti-TNFα drugs (results that have been previously published), and additionally describing the treatment patterns with the first anti-TNFα in IBD patients, in a real-world hospital setting in Spain.

Although our study population reflected mostly the overall IBD population, we observed a higher proportion of CD patients included in this study. A plausible explanation for this could be that a higher proportion of UC patients can be satisfactorily controlled by conventional anti-inflammatory drugs, such as aminosalicylates [21], and hence, those patients were not eligible for the study. Likewise, UC is generally seen as a less progressive and severe disease, which is why in many countries the rate of biologic treatment is lower in UC versus CD.

The median time between IBD diagnosis and first anti-TNFα prescription, approximately 3.5 years, was longer than that reported in other published studies [22,23]. However, we have to consider that this study reflects the clinical practice at the time the study data were collected (first anti-TNFα administration between 2011 and 2013), and that, in recent years, the IBD treatment paradigm has shifted towards an earlier use of biologics in the course of the disease, especially in IBD patients with a worse prognosis. In addition, an earlier treatment with anti-TNFα

therapies is currently favored by the availability of IFX and ADA biosimilars [24].

Although our study results showed no difference in the drug of choice in CD patients (ADA or IFX), we observed a more frequent use of IFX in UC patients, that suggests a preference towards IFX in UC, especially in more severe UC patients. However, these results may also reflect to some extent the different time frames of the marketing authorization for IFX and ADA for UC in Spain. Whereas this was granted in 2007 for IFX, ADA was approved for UC only in 2012, which means ADA only became available for UC during the study enrollment period.

We observed that approximately one-third of biologic-naive patients with IBD who initiated anti-TNFα therapy (either IFX or ADA) required treatment intensification and that the time to treatment intensification was significantly shorter for UC compared to CD patients. An earlier need for treatment intensification in UC patients has also been reported in other retrospective studies [25–27]. Some reasons have been postulated to explain these differences between UC and CD patients, such as a higher inflammatory burden in UC than in CD, a diverse pharmacokinetic profile depending on the type of IBD with a faster clearance in UC patients, or different serum anti-TNFα levels between UC patients and CD patients [25]. In any case, the shorter time to treatment intensification in UC patients observed in our study appears to be driven by a shorter time to intensification with ADA compared to IFX in this condition. Although the difference in the time to treatment intensification between ADA- and IFX-treated patients in UC did not reach statistical significance, the survival curves for ADA and IFX showed markedly different trends along the first 20 months after therapy initiation, consistent with a shorter median time to treatment intensification with ADA (2.4 months) than with IFX (6.3 months). Possibly, the limited size of the UC cohort treated with ADA might have hampered the statistical power to compare time to treatment intensification between both anti-TNFα drugs in UC. It is interesting to note that, possibly, IFX preference for the management of UC may be related, at least in part, with the longer time to intensification with this anti- TNFα. In any case, the observed trends are aligned with those reported in a recent retrospective claims database study; treatment intensification was performed earlier for patients on ADA than for those on IFX [28].

The observed early need of treatment intensification with ADA in UC patients has important practical implications. Given the dosing scheme with ADA, this means that a large proportion of biologic-naive UC patients will require to be dosed with weekly ADA , within only a few months after treatment initiation. Actually, a lower response to ADA has been also observed in pivotal UC trials with the drug, such as the ULTRA studies [29–33].

Approximately 40% of the study population discontinued anti-TNFα treatment over time due to reasons other than remission. The discontinuation rates for CD and UC patients, as well as the time to discontinuation, were similar. These findings are consistent with the results from other observational studies [13,14,34,35]. Although in our study the percentages of CD patients who discontinued either IFX or ADA were comparable, in patients with UC, discontinuation rates among ADA-treated patients were markedly higher than those observed in IFX-treated patients. The high proportion of patients who discontinued treatment with the first anti-TNFα clearly shows how heterogeneous and hard to treat IBD is, as well as the relevance of identifying reliable predictive factors of efficacy, in order to further advance towards a personalized medicine approach. In this regard the HLA-DQA1*05 allele is emerging as a potential marker to select appropriate candidates for anti-TNFα therapies [36].

Consistent with several previous studies[37–40], the time to treatment discontinuation did not significantly differ between IFX-treated patients and ADA-treated CD patients ; however, in patients with UC, the time to treatment discontinuation was significantly longer among patients treated with IFX than ADA.

The results regarding the discontinuation rates and time to discontinuation with ADA in UC patients suggest that perhaps the standard dose regimen approved for ADA in this indication might not be optimal. In fact, the SERENE studies were designed to determine whether an intensified regimen with ADA might improve the efficacy results in patients with IBD. In SERENE-UC, clinical remission at week 52 was numerically higher in patients receiving ADA every week compared with ADA every other week, although the difference was not statistically significant [41]. Similarly, in SERENE-CD, there were no significant differences between the standard and an intensified induction dosing scheme concerning the rates of clinical remission at week 4 and of endoscopic response at week 12 [42].

In any case, in our study, ADA results in the UC cohort should be interpreted cautiously due to the limited number of patients included in this subgroup [20]. These results are somewhat in accordance with those of other published retrospective analyses where UC patients treated with ADA showed higher, albeit not statistically significant, treatment discontinuation rates than those treated with IFX [18,43-46].

Interestingly, although in the majority of patients the reason for treatment discontinuation was a lack of or insufficient efficacy (PNR, LOR, or PR), almost 90% of these patients were switched to a second anti-TNFα. A meta-analysis has shown that, after the failure of an anti-TNFα, the probability of remission using a second anti-TNFα substantially decreases, and the efficacy of the second anti-TNFα clearly depends on the reason for switching treatment, with the highest remission rates for patients with drug intolerance (61%) and the lowest for patients with PNR (30%) or LOR (45%) [47]. Therefore, a sensible approach after the failure of the first anti-TNFα could be to switch to another biologic with a different mode of action [48], especially in IBD patients with PNR or LOR [49,50]. Nevertheless, therapeutic drug level monitoring, when available, may be useful in guiding decisions related to the type of biologic to use after the failure of the first anti-TNFα.

In any case, we should consider that our data on the biologic selected after the failure of the first anti-TNFα are at a large extent conditioned by the marketing approval dates of the newer biologics (in Spain vedolizumab became available for CD and UC in 2015, ustekinumab for CD in 2017), as well as by the commercialization of some biosimilars; furthermore, we cannot discard that the availability of those biosimilars might have influenced on a therapy switching habit.

This study has some key strengths. It provides an estimation of the times to either therapy intensification or discontinuation in biologic-naive patients with IBD, who are prescribed the most frequently used biologic treatments (anti-TNF), based on clinical rather than on administrative data. In addition, this study was conducted in a relatively large sample of patients and, importantly, over a long follow-up period (i.e. 5 years). The major limitations of this study are its observational and retrospective design. The time period covered by our study, with anti-TNFα treatments starting between 2011 and 2013, poses another limitation, as it is possible that some treatment patterns may have changed to some extent over time. Therefore, larger prospective controlled studies are needed to confirm our results.

In conclusion, our study results suggest that, despite the extended use of anti-TNFα drugs as a first-line treatment for CD and UC following conventional therapy failure, this therapeutic option is associated with relatively high rates of treatment intensification and discontinuation. Therefore, a substantial proportion of IBD patients could benefit from alternative first-line biologic therapies. To

select the most appropriate IBD treatment it would be essential to identify biomarkers able to predict the long-term success with the different available biologic agents.

Data availability statement

The data that support the findings of this study are available from the sponsor upon request

Conflict of Interest

Guillermo Bastida has received a speaker honorarium from Abvvie, Pfizer, Janssen, FAES, Takeda, Tillots and Abbott. Also, Guillermo Bastida has participated in Scientific Advisory Comitees of Takeda, Janssen and Abvvie. Ignacio Marín-Jiménez has served as a consultant, advisory member, speaker, or has received research funding from MSD, Abbvie, Takeda, Tillots, Ferring, Falk-Pharma, Faes Farma, UCB Pharma, Otsuka Pharmaceutical, Shire, Gebro Pharma, and Chiesi. Ana Forés has nothing to declare. Esther García-Planella has served as a speaker or received research or educational funding or advisory fees from MSD, Abbvie, Jansen, Ferring, Shire, Tillots, Faes. Federico Argüelles-Arias has served as a speaker, a consultant and as an advisory member for or have received research funding from Janssen, MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Sandoz, Takeda, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Gebro Pharma, Amgen and Vifor Pharma. Ignacio Tagarro, Alonso Fernandez-Nistal, Carmen Montoto and Jesús Aparicio are full employees of Takeda Farmacéutica España. Mariam Aguas has served as a speaker for MSD, Abbvie, Janssen, Takeda and Tillots, and received educational grants from Janssen, MSD and Abbvie. Javier Santos-Fernández has nothing to declare. Marta Maia Bosca-Watts declares educational activities, research projects, scientific meetings and advisory boards sponsored by MSD, Ferring, Abbvie, Janssen and Takeda. Rocío Ferreiro-Iglesias has served as a speaker for or has received research funding from Takeda, MSD, Abbvie, Janssen, Palex, Shire Pharmaceuticals, TillottsPharma and Casenrecordati. Olga Merino has nothing to declare. Xavier Aldeguer has nothing to declare. Xavier Cortes has nothing to declare. Beatriz Sicilia has nothing to declare. Francisco Mesonero has served as a speaker or consultant from MSD, Takeda, Janssen, Abbvie and Ferring. Manuel Barreiro-de Acosta has served as a speaker, a consultant and advisory board member for, or has received research funding from, MSD, Abbvie, Janssen, Pfizer, Kern Pharma, Biogen, Takeda, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Gebro Pharma, Otsuka Pharmaceutical and Vifor Pharma.

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