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Impact of Prior Biologic Mechanism of Action on Anti-TNF Effectiveness in Inflammatory Bowel Disease: An ENEIDA Registry Study

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ABSTRACT

Background: The expanding use of targeted therapies in inflammatory bowel disease has made treatment sequencing increasingly relevant, yet evidence on anti-TNF effectiveness after prior biologics with different mechanisms of action (MOA) remains limited. Our objective is to evaluate the durability of anti-TNF treatment in this scenario.

Methods: Multicentre study based on data from the ENEIDA registry. Patients who received second-line anti-TNF therapy after a first biologic with a different MOA for active luminal disease were identified. Using propensity score matching, each case was matched with three controls from two cohorts: patients treated with second-line anti-TNF after another anti-TNF and patients receiving first-line anti-TNF therapy. Treatment durability and short- and long-term clinical effectiveness were assessed.

Results: Sixty-six Crohn's disease patients and 117 UC patients receiving anti-TNF after other MOA were included. In CD, second-line anti-TNF therapy after a different MOA (62% ustekinumab) was associated with a higher risk of treatment discontinuation compared with first-line anti-TNF therapy (HR 1.55; 95% CI, 1.05–2.30), without significant differences in short- or

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long-term clinical effectiveness. In UC, anti-TNF therapy after a different MOA (90% vedolizumab) was associated with lower treatment durability compared with first-line anti-TNF therapy (HR 1.69; 95% CI, 1.31–2.19) and with anti-TNF after another anti-TNF agent (HR 1.91; 95% CI, 1.48–2.48), its remission rates significantly lower at both short- and long-term follow-up ($p < 0.001$). **Conclusions:** Anti-TNF therapy used after a different MOA is associated with reduced effectiveness and durability compared with its use as first-line therapy or after another anti-TNF agent, especially in UC.

1 | Introduction

The therapeutic landscape of inflammatory bowel disease (IBD) has expanded substantially over the past decade with the introduction of multiple biologic agents and small molecules targeting distinct inflammatory pathways [1]. While this diversification has enabled a more individualized approach to treatment, it has also introduced uncertainty regarding the optimal sequencing of available therapies [2, 3]. In routine clinical practice, treatment decisions are essentially guided by disease phenotype, prior drug exposure, safety considerations, and the presence of complications such as perianal disease or extraintestinal manifestations, rather than by robust comparative sequencing data [4].

Anti-tumour necrosis factor (anti-TNF) agents remain a cornerstone in the management of moderate-to-severe IBD due to their well-established efficacy, rapid onset of action and proven benefit in complex disease scenarios, including fistulizing Crohn's disease (CD) [5], acute severe ulcerative colitis (UC) and extraintestinal manifestations [6]. However, in the current therapeutic era, many patients initiate treatment with biologics or targeted therapies with alternative mechanisms of action, such as anti-integrins or interleukin-12/23 or interleukin-23 inhibitors, particularly in the context of safety concerns, comorbidities, or physician and patient preferences.

Although anti-TNF therapies are traditionally positioned as first-line biologic agents, a subset of patients may require anti-TNF treatment after failure or suboptimal response to a first-line non-anti-TNF biologic. This scenario, while still relatively infrequent, reflects the clinical complexity of IBD and may arise due to persistent luminal activity, development or progression of perianal disease, emergence of extraintestinal manifestations, or the need for rapid and potent inflammatory control. Despite its clinical relevance, evidence supporting the efficacy of anti-TNF treatment when used as a second-line option after a different mechanism of action (MOA) is virtually non-existent.

Indirect data can be drawn from sequencing-focused cohorts and post hoc subgroup analyses of pivotal trials, which suggest that effectiveness of advanced therapies is modulated by treatment position and by the MOA previously employed [7–10]. However, these analyses have almost exclusively evaluated non-anti-TNF agents positioned after anti-TNF failure, leaving the reverse and increasingly frequent sequence—anti-TNF after a different MOA—essentially unexplored. As a result, clinicians currently lack high-quality real-world data to inform decision-making in this increasingly encountered therapeutic pathway. This clinical situation is and will continue to be increasingly common in the future. Far from considering anti-TNF drugs as minor alternatives compared to new therapeutic alternatives, they undoubtedly retain their usefulness in some of the most complex cases of the disease.

The aim of the present study was to evaluate effectiveness and durability of anti-TNF therapy when used as second-line treatment after exposure to a biologic agent with a different MOA in patients with IBD, providing real-world evidence to support therapeutic sequencing in complex clinical scenarios.

2 | Methods

2.1 | Study Design

This was a multicenter, observational study based on the ENEIDA registry, a nationwide database promoted by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) [11]. ENEIDA is a prospectively maintained registry that at the time of the present study, included more than 87,000 patients from 85 Spanish hospitals.

2.2 | Study Population

Three cohorts of adult patients (≥ 18 years) with an established diagnosis of CD or UC, according to European Crohn's and Colitis Organisation (ECCO) criteria, were included.

Only patients with complete data were included in the analysis, including baseline characteristics, treatment start and end dates, treatment status regarding discontinuation and the specific anti-TNF agent used.

The cohort of interest comprised patients with IBD who received an anti-TNF agent for active UC or CD luminal disease as second-line therapy after prior treatment with a non-anti-TNF biologic with a different MOA between January 2018 and January 2025. This time window was defined to ensure data quality and to avoid historical cohort bias. In addition, during this period several approved therapeutic alternatives were available, preventing treatment persistence driven solely by the lack of other options. Two control cohorts were defined for each disease (CD and UC):

1. Patients who received anti-TNF therapy but as first-line biologic treatment.
2. Patients who received anti-TNF therapy also as second-line treatment, but following another first-line anti-TNF agent.

Across all cohorts, patients who initiated anti-TNF therapy for CD perianal disease, postoperative recurrence prevention, pouchitis, extraintestinal manifestations or other immune-mediated diseases were excluded. These indications were excluded because the study was designed to assess *luminal* effectiveness, evaluated through luminal durability and clinical activity indices (partial Mayo score and HBI). Perianal and

other non-luminal indications require distinct outcome measures (e.g., fistula drainage or closure) and would not be adequately captured by luminal endpoints; in addition, perianal CD represents a scenario in which anti-TNF agents carry first-line-level evidence, which could confound a comparison focused on luminal sequencing.

All treatments were prescribed according to routine clinical practice using standard dosing regimens. Dose escalation or treatment intensification was not considered treatment failure provided that the patient continued receiving the same anti-TNF agent.

2.3 | Data Collection

All study variables were extracted directly from the ENEIDA registry. Collected data included disease extent or location, Montreal classification for CD, prior surgical history, smoking status, concomitant immunomodulator use, and the presence of extraintestinal manifestations or perianal disease, among others. All patients had provided written informed consent prior to inclusion in the registry. The ENEIDA registry was approved by the Research Ethics Committee at all the participating centres.

2.4 | Outcomes and Definitions

The primary outcome was treatment durability, assessed through treatment persistence free from discontinuation or treatment failure. Treatment persistence was selected as the primary outcome because it represents a robust, pragmatic surrogate of real-world effectiveness and safety.

Treatment failure was defined as the recording of primary or secondary failure in the registry, or the need for a switch to another biologic agent or luminal surgery for UC or CD. Secondary failure was defined as the need for a treatment change or luminal surgery owing to worsening inflammatory activity after an initial therapeutic response.

Surgery for perianal disease, dose escalation, or treatment intensification was not considered treatment failure if the patient remained on the same anti-TNF agent. All treatment discontinuations were counted as treatment failure and included in the persistence analysis irrespective of the reason. Discontinuations attributable to adverse events, including treatment intolerance, were additionally analysed separately as a safety outcome.

Secondary objectives included short- and long-term rates of clinical response and remission and safety. Clinical response and remission were recorded in ENEIDA according to the treating investigator's judgement; the partial Mayo and Harvey–Bradshaw Index thresholds below are provided as a reference framework and were not necessarily calculated prospectively for each visit: clinical remission is defined as a partial Mayo score [12] < 2 with a rectal bleeding sub score of 0 for UC, and a Harvey–Bradshaw Index [13] < 5 for CD. Clinical response was defined as a reduction of ≥ 3 points and at least a

30% decrease from baseline in the partial Mayo score for UC, and a decrease of ≥ 3 points in the HBI for CD, without reaching remission thresholds. Clinical effectiveness was evaluated at short term (Week 16 $\pm$ 2) and long term (Week 52 $\pm$ 2).

2.5 | Statistical Analysis

Quantitative variables were described as mean and standard deviation (SD) when normally distributed, or as median and interquartile range (IQR) otherwise. Qualitative variables were expressed as absolute and relative frequencies (%). Normality was assessed using the Kolmogorov–Smirnov or Shapiro–Wilk tests depending on sample size and variable type.

Baseline characteristics were compared across treatment groups using the Chi-square test or Fisher's exact test when appropriate. Quantitative variables were compared using one-way ANOVA or, when normality was not met, the Kruskal–Wallis test.

Treatment persistence was evaluated through survival analyses using Kaplan–Meier curves, considering discontinuation for any cause as the event. Differences between curves were analysed with the log-rank test. All tests were two-sided and a p -value < 0.05 was considered statistically significant.

To minimize confounding and balance baseline characteristics between comparison groups, propensity score matching was performed. The probability of belonging to the 'anti-TNF after another MOA' group was estimated using separate logistic regression models for CD and UC. Covariates were selected a priori based on clinical relevance as recognized prognostic factors and potential confounders of treatment allocation and outcome, rather than through automated, data-driven selection.

For CD, the model included sex, Montreal classification (age at diagnosis, disease location, presence of L4 involvement and disease behaviour), categorized disease duration (< 12 vs. ≥ 12 months), smoking status, presence of extraintestinal manifestations, presence of perianal disease, prior abdominal surgery, type of anti-TNF agent used and concomitant immunomodulator therapy.

For UC, the model included sex, categorized age (< 60 vs. ≥ 60 years), categorized disease duration (< 12 vs. ≥ 12 months), disease extent according to Montreal, smoking status, presence of extraintestinal manifestations, concomitant immunomodulator use and type of anti-TNF agent used.

Covariate balance after propensity score matching was assessed using standardized mean differences (SMDs) for all variables included in the propensity score model. SMDs were calculated before and after matching, and an absolute SMD < 0.10 was considered indicative of adequate covariate balance. To facilitate visual assessment, covariate balance was also evaluated using a Love plot displaying the absolute SMDs for each baseline variable before and after matching.

For the cohort of anti-TNF after another anti-TNF, the reason for discontinuing the previous treatment was also considered for both CD and UC.

Each case in the 'anti-TNF after another MOA' group was subsequently matched without replacement to six controls—three from the 'anti-TNF after anti-TNF' group and three from the 'first-line anti-TNF' group—using nearest-neighbour matching. A calliper width of 0.2 standard deviations of the logit of the propensity score was applied, with calliper relaxation allowed only when insufficient suitable controls were available to maintain the 1:6 matching ratio.

To account for the residual imbalance observed after matching and to provide adjusted effect estimates, a multivariable Cox proportional-hazards model was fitted on the matched cohorts for the primary outcome of treatment persistence, in each disease separately. Covariates were selected a priori on clinical grounds and included treatment group (the main exposure), age, smoking status, concomitant immunomodulator use, type of anti-TNF agent, and disease extent (Montreal E) in UC or disease phenotype (Montreal behaviour) in CD. Given the limited number of events in some matched subgroups—particularly CD treated with anti-TNF after a different mechanism of action—a corresponding multivariable model for clinical effectiveness was not fitted, to avoid overfitting; short-term effectiveness is therefore reported descriptively.

Missing or unevaluable clinical effectiveness data at Week 16 or Week 52 were not imputed and were not classified as non-response. Instead, patients without available assessment were reported as a separate 'not available' category, and proportions were calculated using the total number of patients in each matched cohort as the denominator.

3 | Results

In the ENEIDA registry, 32,244 patients are recorded as having received at least one biologic therapy, of whom 66 patients with CD and 117 patients with UC treated with a second-line anti-TNF agent after a biologic with a different MOA were included. These patients were matched to two control cohorts, resulting in 198 matched patients in CD and 351 matched patients in UC.

Propensity score matching substantially improved the comparability of baseline characteristics between groups. Before matching, several baseline covariates showed meaningful imbalance, whereas after matching the standardized mean differences were markedly reduced across all variables included in the propensity score model. After matching, all covariates achieved adequate balance (standardized mean difference <0.10), with the exception of age, which improved substantially (from 0.72 to 0.20) but retained a residual imbalance. Those data are shown in Figure S1.

As shown in Table 1, no significant differences in baseline characteristics were observed among the three cohorts for either disease, indicating adequate balance after propensity score matching.

The median follow-up was 30 (IQR 13–120), 52 (IQR 21–130) and 51 (IQR 17–120) months in the anti-TNF after a different MOA, anti-TNF after anti-TNF and first-line anti-TNF cohorts, respectively, in UC, and 41, 61 and 77 months, respectively, in CD.

Among patients with CD treated with an anti-TNF after another MOA, the predominant disease phenotype was inflammatory (68%). A history of perianal disease was present in 27% of patients, and 29% had undergone prior abdominal surgery.

In the UC cohort, most patients had extensive colitis (52%), and 21% presented with extraintestinal manifestations at baseline.

Among patients in the anti-TNF-after-anti-TNF cohort, the most frequently used prior agent was adalimumab (54%) followed by infliximab (46%) in CD and infliximab (44%) followed by adalimumab (37%) and golimumab (19%) in UC. In contrast, among patients previously exposed to a biologic with a different MOA, most patients with CD had been treated with ustekinumab (62%) followed by vedolizumab (38%), whereas most patients with UC had received vedolizumab (90%) followed by ustekinumab (10%).

3.1 | Treatment Persistence

In patients with CD, the use of an anti-TNF agent after a different MOA was associated with significantly shorter treatment persistence compared with first-line anti-TNF therapy (HR 1.55; 95% CI, 1.05–2.30), but with no significant differences compared with anti-TNF use after another anti-TNF agent (HR 1.19; 95% CI, 0.81–1.75), as shown in Figure 1.

In patients with UC, treatment with an anti-TNF agent after a different MOA was associated with a significantly shorter treatment persistence compared with both first-line anti-TNF therapy (HR 1.69; 95% CI, 1.31–2.19) and anti-TNF therapy following another anti-TNF agent (HR 1.91; 95% CI, 1.48–2.48). These findings are illustrated in Figure 2.

The multivariable Cox models for treatment persistence are shown in Table 2. In UC, anti-TNF therapy after a different mechanism of action was independently associated with a higher risk of discontinuation than anti-TNF after another anti-TNF agent (aHR 1.89, 95% CI 1.45–2.45, $p < 0.001$), with no significant contribution from the remaining covariates. In CD, treatment group was not independently associated with persistence (anti-TNF after a different MOA: aHR 1.23, 95% CI 0.83–1.81, $p = 0.301$), nor was any other covariate.

3.2 | Short- and Long-Term Rates of Clinical Effectiveness

In CD patients, no significant differences were observed among the three cohorts (second line therapy with anti-TNF after a different MOA, first-line anti-TNF therapy or anti-TNF use after another anti-TNF agent), at either short-term or long-term rates of clinical effectiveness. In contrast, among patients with UC, the use of an anti-TNF agent after a different MOA was associated with significantly lower rates of clinical remission at both short-term follow-up (20% vs. 34% vs. 39%, $p < 0.001$) and long-term follow-up (18% vs. 34% vs. 42%, $p < 0.001$) compared with the other two cohorts. All effectiveness outcomes are summarized in Table 3.

The rate of treatment intensification during follow-up was comparable across the three groups, both in patients with UC (25%

TABLE 1 | Baseline characteristics according to the type of inflammatory bowel disease.

Crohn's disease					
	AntiTNF after other MOA (N=66)	AntiTNF after other antiTNF (N=198)	First line antiTNF (N=198)	Total (N=462)	p
Sex, female	34 (51.5%)	102 (51.5%)	103 (52%)	239 (51.7%)	0.994
Age, years	53.4 (18.7)	51.8 (16.5)	53.5 (16.9)	52.7 (17)	0.571
Montreal, age					
A1	7 (10.6%)	15 (7.6%)	16 (8.1%)	38 (8.2%)	0.413
A2	18 (27.3%)	74 (37.4%)	59 (29.8%)	151 (32.7%)	
A3	41 (62.1%)	109 (55.1%)	123 (62.1%)	273 (59.1%)	
Montreal, location					
L1	35 (53%)	112 (56.6%)	110 (55.6%)	257 (55.6%)	0.946
L2	10 (15.2%)	26 (13.1%)	31 (15.7%)	67 (14.5%)	
L3	21 (31.8%)	60 (30.3%)	57 (28.8%)	138 (29.9%)	
L4	18 (27.3%)	50 (25.3%)	51 (25.8%)	119 (25.8%)	0.949
Montreal, behaviour					
B1	45 (68.2%)	141 (71.2%)	141 (71.2%)	327 (70.8%)	0.747
B2	19 (28.8%)	50 (25.3%)	46 (23.2%)	115 (24.9%)	
B3	2 (3%)	7 (3.5%)	11 (5.6%)	20 (4.3%)	
Perianal disease	18 (27.3%)	42 (21.2%)	46 (23.2%)	106 (22.9%)	0.593
EIMs	18 (27.3%)	46 (23.2%)	45 (22.7%)	109 (23.6%)	0.744
Prior luminal surgery	19 (28.8%)	71 (35.9%)	54 (27.3%)	144 (31.2%)	0.165
Smoking habit					
Former	14 (21.2%)	33 (16.7%)	39 (19.7%)	86 (18.6%)	0.836
Never	39 (59.1%)	126 (63.6%)	116 (58.6%)	281 (60.8%)	
Current	13 (19.7%)	39 (19.7%)	43 (21.7%)	95 (20.6%)	
Reason for discontinuation of the previous drug					
Non primary response	11 (16.7%)	41 (20.7%)	NA	NA	0.659
Secondary loss of response	31 (47%)	97 (49%)	NA	NA	
Adverse event	7 (10.6%)	13 (6.6%)	NA	NA	
Other	17 (25.8%)	47 (23.7%)	NA	NA	
Disease duration	90.5 (110.6)	104.8 (102.6)	92.2 (127.8)	97.3 (115.1)	0.483
Concomitant immunomodulator	16 (24.2%)	44 (22.2%)	37 (18.7%)	97 (21%)	0.539
Ulcerative colitis					
	AntiTNF after other MOA (N=117)	AntiTNF after AntiTNF (N=351)	First line antiTNF (N=351)	All (N=819)	p
Sex, female	52 (44.4%)	152 (43.3%)	160 (45.6%)	364 (44.4%)	0.831
Age, years	54.3 (19.8)	49.6 (16.6)	53.2 (17.7)	51.8 (17.7)	0.006

(Continues)

TABLE 1 | (Continued)

Ulcerative colitis					
	AntiTNF after other MOA (N = 117)	AntiTNF after AntiTNF (N = 351)	First line antiTNF (N = 351)	All (N = 819)	p
Extension					
E1	8 (6.8%)	20 (5.7%)	23 (6.6%)	51 (6.2%)	0.492
E2	48 (41%)	132 (37.6%)	153 (43.6%)	333 (40.7%)	
E3	61 (52.1%)	199 (56.7%)	175 (49.9%)	435 (53.1%)	
EIMs	25 (21.4%)	84 (23.9%)	73 (20.8%)	182 (22.2%)	0.590
Smoking habit					
Former	20 (17.1%)	42 (12%)	55 (15.7%)	117 (14.3%)	0.412
Never	91 (77.8%)	287 (81.8%)	281 (80.1%)	659 (80.5%)	
Current	6 (5.1%)	22 (6.3%)	15 (4.3%)	43 (5.3%)	
Reason for discontinuation of the previous drug					
Non primary response	27 (23.1%)	68 (19.4%)	NA	NA	0.289
Secondary loss of response	60 (51.3%)	184 (52.4%)	NA	NA	
Adverse event	4 (3.4%)	29 (8.3%)	NA	NA	
Other	26 (22.2%)	70 (19.9%)	NA	NA	
Drug					
Adalimumab	15 (12.8%)	46 (13.1%)	41 (11.7%)	102 (12.5%)	0.834
Golimumab	4 (3.4%)	16 (4.6%)	11 (3.1%)	31 (3.8%)	
Infliximab	98 (83.8%)	289 (82.3%)	299 (85.2%)	686 (83.8%)	
Disease duration	120.5 (116.2)	128.5 (111.2)	122.1 (117.3)	124.7 (114.5)	0.698
Concomitant immunomodulator	17 (14.5%)	55 (15.7%)	48 (13.7%)	120 (14.7%)	0.756

Abbreviations: EIMs, extra intestinal manifestations; IMM, immunomodulator; NA, not applicable.

vs. 21% vs. 25%, $p = 0.204$) and in those with CD (28% vs. 25% vs. 29%, $p = 0.749$).

Regarding safety outcomes, no significant differences were observed among the three cohorts in either patients with CD or those with UC. Similarly, no significant differences were found in the rate of treatment discontinuation due to adverse events across the three groups. Safety outcomes are summarized in Table 4.

4 | Discussion

In this nationwide, propensity-matched study, anti-TNF therapy used after a biologic with a different MOA showed reduced treatment durability compared with first-line anti-TNF in both CD and UC, and compared with anti-TNF used after another anti-TNF in UC. Reduced short- and long-term clinical effectiveness was significant in UC but not in CD, and the differences were not attributable to safety events.

Anti-TNF agents represented a breakthrough in the treatment of IBD and have been extensively used for more than three decades. Although they are most prescribed as first-line biologic therapy, their use after exposure to agents with a different MOA has become increasingly frequent in contemporary clinical practice. This shift reflects the growing complexity of IBD management and the wide range of clinical scenarios that may prompt treatment modification, including therapeutic failure, development of perianal disease, or the appearance of extraintestinal manifestations.

Despite the clinical relevance of therapeutic sequence, evidence regarding the effectiveness of anti-TNF therapy following prior exposure to a different MOA has been lacking, both from randomized controlled trials and from real-world clinical practice. The present study addresses this gap and shows that the use of anti-TNF agents after a different MOA is associated with lower treatment durability than its use as first-line therapy. This pattern was more consistent in UC, where it also affected clinical effectiveness, whereas in CD it

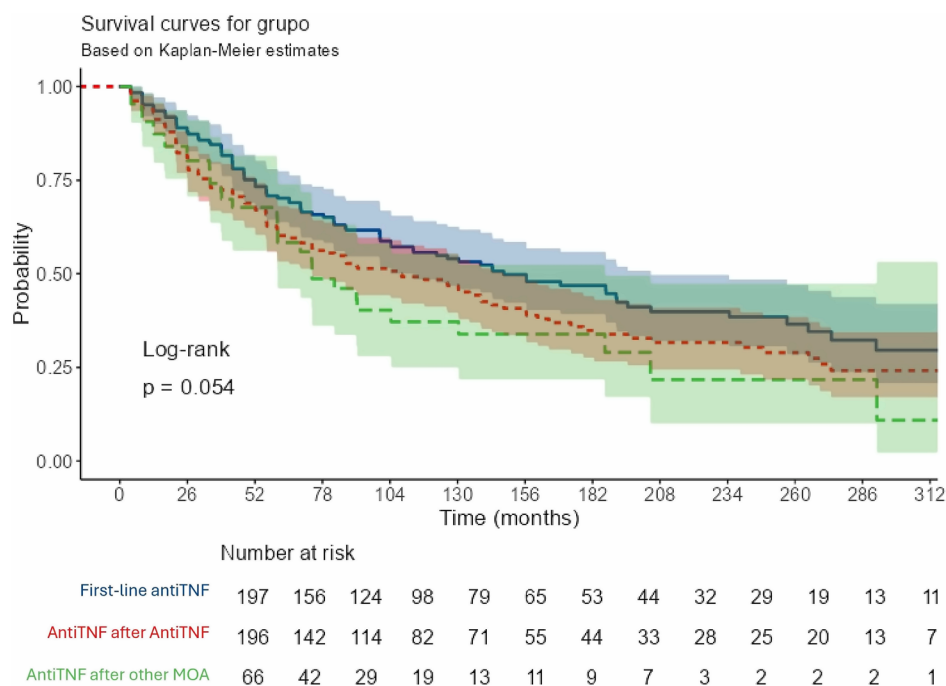


FIGURE 1 | Treatment persistence in patients with Crohn's disease.

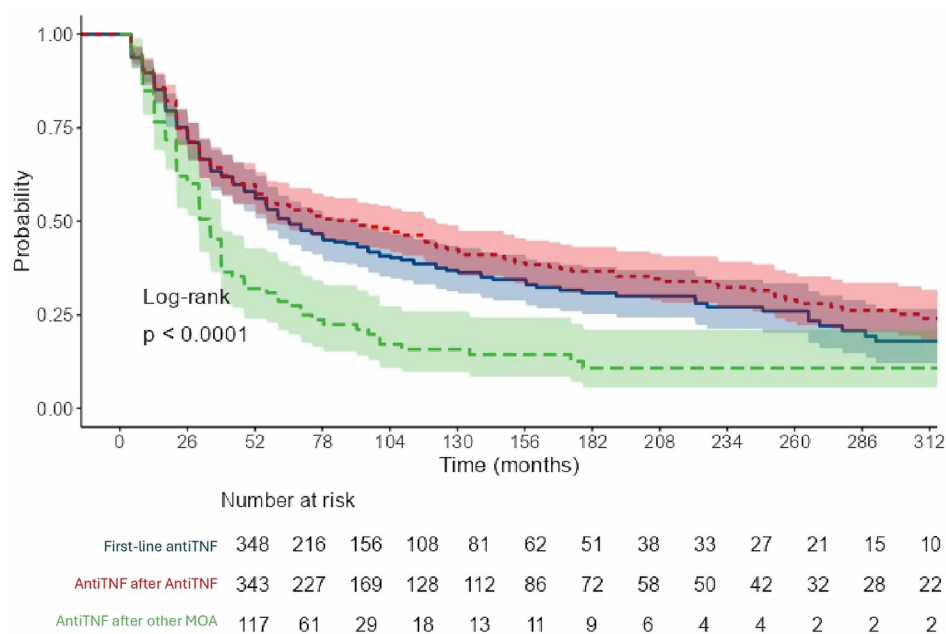


FIGURE 2 | Treatment persistence in patients with ulcerative colitis.

was confined to reduced durability relative to first-line therapy. Importantly, this reduced durability does not appear to be driven by a higher incidence of adverse events in a potentially more fragile population, but rather by reduced clinical effectiveness, as detailed below.

Several factors may account for the more consistent detrimental effect observed in UC. The prior agent differed substantially between diseases: most UC patients had been exposed to vedolizumab, a gut-selective anti-integrin, whereas most CD patients had received ustekinumab, an IL-12/23 inhibitor. These mechanisms may shape the residual mucosal immune

environment in different ways, potentially conditioning the subsequent response to TNF blockade. Beyond the prior drug, intrinsic differences in disease biology and in the positioning of advanced therapies between UC and CD—including the predominant first-line use of vedolizumab in UC versus ustekinumab in CD—may also contribute. These considerations are hypothesis-generating and require confirmation in dedicated translational studies.

The evidence supporting the effectiveness of anti-TNF agents across multiple IBD settings is extensive. As the longest-established class of targeted therapies for IBD, anti-TNF agents

TABLE 2 | Multivariate Cox models for survival analysis.

Variable		All	HR (univariable)	HR (multivariable)
Crohn disease				
Group	AntiTNF—AntiTNF	198 (43.0)	—	—
	First line antiTNF	197 (42.7)	0.78 (0.59–1.02, $p=0.074$)	0.79 (0.60–1.05, $p=0.104$)
	AntiTNF after other MOA	66 (14.3)	1.22 (0.83–1.79, $p=0.323$)	1.23 (0.83–1.81, $p=0.301$)
Age	Young	265 (57.5)	—	—
	Elderly	196 (42.5)	1.02 (0.79–1.32, $p=0.865$)	0.97 (0.73–1.28, $p=0.814$)
Type of antiTNF	Adalimumab	211 (45.8)	—	—
	Infliximab	250 (54.2)	1.20 (0.92–1.55, $p=0.173$)	1.21 (0.91–1.61, $p=0.199$)
Smoking habit	Former	86 (18.7)	—	—
	Never	280 (60.7)	1.15 (0.82–1.62, $p=0.407$)	1.09 (0.77–1.55, $p=0.608$)
	Current	95 (20.6)	1.41 (0.94–2.11, $p=0.099$)	1.34 (0.88–2.02, $p=0.168$)
Concomitant immunomodulator	No	365 (79.2)	—	—
	Yes	96 (20.8)	0.95 (0.70–1.30, $p=0.769$)	0.85 (0.59–1.22, $p=0.375$)
Montreal behaviour	B1	326 (70.7)	—	—
	B2	115 (24.9)	1.07 (0.81–1.43, $p=0.621$)	1.06 (0.79–1.41, $p=0.690$)
	B3	20 (4.3)	0.77 (0.41–1.47, $p=0.436$)	0.77 (0.40–1.49, $p=0.439$)
Ulcerative colitis				
Group	AntiTNF—AntiTNF	345 (43.1)	—	—
	First line antiTNF	341 (42.6)	1.14 (0.93–1.39, $p=0.197$)	1.13 (0.92–1.39, $p=0.230$)
	AntiTNF after other MOA	114 (14.2)	1.89 (1.45–2.45, $p<0.001$)	1.89 (1.45–2.45, $p<0.001$)
Age	Young	448 (56.0)	—	—
	Elderly	352 (44.0)	1.10 (0.92–1.32, $p=0.296$)	1.03 (0.85–1.26, $p=0.739$)
Type of antiTNF	Adalimumab	102 (12.8)	—	—
	Golimumab	31 (3.9)	1.08 (0.66–1.78, $p=0.749$)	1.10 (0.66–1.83, $p=0.726$)
	Infliximab	667 (83.4)	0.94 (0.72–1.23, $p=0.644$)	0.90 (0.68–1.19, $p=0.471$)
Smoking habit	Former	117 (14.6)	—	—
	Never	640 (80.0)	0.88 (0.69–1.13, $p=0.317$)	0.86 (0.66–1.12, $p=0.256$)
	Current	43 (5.4)	0.67 (0.41–1.08, $p=0.100$)	0.65 (0.39–1.07, $p=0.092$)
Concomitant immunomodulator	No	681 (85.1)	—	—
	Yes	119 (14.9)	1.05 (0.83–1.34, $p=0.668$)	1.06 (0.83–1.37, $p=0.635$)
Montreal extension	E1	51 (6.4)	—	—
	E2	326 (40.8)	0.94 (0.64–1.39, $p=0.749$)	0.92 (0.62–1.37, $p=0.683$)
	E3	423 (52.9)	0.88 (0.60–1.30, $p=0.524$)	0.87 (0.59–1.29, $p=0.492$)

benefit from unparalleled real-world experience and robust data from pivotal registration trials [14, 15], as well as from more recent comparative studies [16, 17]. Beyond luminal disease activity, anti-TNF therapies remain the advanced treatments with the strongest supporting evidence in complex clinical scenarios, including fistulizing CD [18, 19], acute severe UC [20], perianal CD [21] and a wide range of extraintestinal manifestations, particularly musculoskeletal involvement [22, 23].

However, a common limitation across this body of evidence is that anti-TNF agents are almost invariably evaluated either as first-line biologic therapy or after failure of another anti-TNF agent. In fact, in the case of anti-TNF, most clinical trials—including registration studies—are restricted to biologic-naïve populations [24–26]. Consequently, data on the performance of anti-TNF agents after exposure to other therapeutic targets are scarce. Experience with newer advanced therapies has highlighted the importance of

TABLE 3 | Clinical effectiveness at short and long term according to inflammatory bowel disease subtype.

Crohn's disease					
	AntiTNFAfter other MOA (N = 54)	AntiTNF after AntiTNF (N = 150)	First-line antiTNF (N = 152)	p value antiTNF-antiTNF vs. other MOA-antiTNF	p value first-line antiTNF vs. other MOA-antiTNF
Clinical effectiveness at Week 16					
Non primary response	6 (9.1%; 95% CI 3.4%–18.7%)	19 (9.6%; 95% CI 5.9%–14.6%)	11 (5.6%; 95% CI 2.8%–9.7%)	0.983	0.498
Clinical response	18 (27.3%; 95% CI 17.0%–39.6%)	45 (22.7%; 95% CI 17.1%–29.2%)	36 (18.2%; 95% CI 13.1%–24.3%)		
Clinical remission	20 (30.3%; 95% CI 19.6%–42.9%)	54 (27.3%; 95% CI 21.2%–34.0%)	72 (36.4%; 95% CI 29.7%–43.5%)		
Not available	22 (33.3%; 95% CI 22.2%–46.0%)	80 (40.4%; 95% CI 33.5%–47.6%)	79 (39.9%; 95% CI 33.0%–47.1%)		
Clinical effectiveness at Week 54					
None primary response	4 (6.1%; 95% CI 1.7%–14.8%)	13 (6.6%; 95% CI 3.5%–11.0%)	9 (4.5%; 95% CI 2.1%–8.5%)	0.859	0.121
Clinical response	18 (27.3%; 95% CI 17.0%–39.6%)	40 (20.2%; 95% CI 14.8%–26.5%)	31 (15.7%; 95% CI 10.9%–21.5%)		
Clinical remission	13 (19.7%; 95% CI 10.9%–31.3%)	46 (23.2%; 95% CI 17.5%–29.7%)	64 (32.3%; 95% CI 25.9%–39.3%)		
Not available	31 (47.0%; 95% CI 34.6%–59.7%)	99 (50.0%; 95% CI 42.8%–57.2%)	94 (47.5%; 95% CI 40.4%–54.7%)		
Ulcerative colitis					
	AntiTNFAfter other MOA (N = 89)	AntiTNF after AntiTNF (N = 261)	First-line antiTNF (n = 250)	p value antiTNF-antiTNF vs. other MOA-antiTNF	p value first-line antiTNF vs. Other MOA- AntiTNF
Clinical effectiveness at Week 16					
Non primary response	19 (16.2%; 95% CI 10.1%–24.2%)	43 (12.3%; 95% CI 9.0%–16.1%)	37 (10.5%; 95% CI 7.5%–14.2%)	0.001	0.027
Clinical response	31 (26.5%; 95% CI 18.8%–35.5%)	62 (17.7%; 95% CI 13.8%–22.1%)	65 (18.5%; 95% CI 14.6%–23.0%)		
Clinical remission	36 (30.8%; 95% CI 22.6%–40.0%)	109 (31.1%; 95% CI 26.2%–36.2%)	134 (38.2%; 95% CI 33.1%–43.5%)		
Not available	31 (26.5%; 95% CI 18.8%–35.5%)	137 (39.0%; 95% CI 33.9%–44.4%)	115 (32.8%; 95% CI 27.9%–37.9%)		
Clinical effectiveness at Week 54					
None primary response	20 (17.1%; 95% CI 10.8%–25.2%)	37 (10.5%; 95% CI 7.5%–14.2%)	39 (11.1%; 95% CI 8.0%–14.9%)	0.001	<0.001
Clinical response	32 (27.4%; 95% CI 19.5%–36.4%)	55 (15.7%; 95% CI 12.0%–19.9%)	50 (14.2%; 95% CI 10.8%–18.3%)		
Clinical remission	21 (17.9%; 95% CI 11.5%–26.1%)	102 (29.1%; 95% CI 24.4%–34.1%)	116 (33.0%; 95% CI 28.1%–38.2%)		
Not available	44 (37.6%; 95% CI 28.8%–47.0%)	157 (44.7%; 95% CI 39.4%–50.1%)	146 (41.6%; 95% CI 36.4%–46.9%)		

TABLE 4 | Adverse events and drug withdrawal rate per adverse event according to inflammatory bowel disease subtype.

Crohn's disease					
	AntiTNF after other MOA (N = 65)	AntiTNF after other antiTNF (N = 198)	First line antiTNF (N = 198)	p First line antiTNF vs. other MOA-antiTNF	p AntiTNF- antiTNF vs. other MOA-antiTNF
Adverse event	8 (12.3%)	31 (15.7%)	41 (20.7%)	0.131	0.501
Drug withdrawal due to adverse event	3 (4.6%)	5 (2.5%)	24 (12.1%)	0.084	0.399
Ulcerative colitis					
	AntiTNF after other MOA (N = 117)	AntiTNF after other antiTNF (N = 261)	First line antiTNF (n = 347)	p First line antiTNF vs. other MOA-antiTNF	p AntiTNF- antiTNF vs. other MOA-antiTNF
Adverse event	22 (18.8%)	54 (15.5%)	43 (12.4%)	0.084	0.406
Drug withdrawal due to adverse event	6 (5.1%)	6 (1.7%)	25 (7.2%)	0.437	0.045

assessing drug behaviour in different lines of therapy, as treatment sequencing appears to have a meaningful impact on effectiveness [27]. For example, available data suggest that ustekinumab may retain greater effectiveness after anti-TNF exposure than vedolizumab [9], while vedolizumab seems to be particularly disadvantaged when used in later lines of treatment [28]. Our results extend this body of evidence to the reverse and less-studied sequence. Whereas prior work has shown that effectiveness of non-anti-TNF agents is reduced when positioned after anti-TNF failure [9, 28], and that drug sequencing overall influences outcomes in large real-world cohorts [27], our data indicate that anti-TNF agents are likewise disadvantaged when used after a different MOA—especially in UC—suggesting that the impact of sequencing is bidirectional and not confined to non-anti-TNF therapies.

Our data show that the use of an anti-TNF agent after prior exposure to a different MOA is associated with reduced treatment persistence in both CD and UC when compared with first-line anti-TNF therapy. However, the pattern differed by disease. In UC, durability was also significantly reduced compared with anti-TNF used after another anti-TNF agent, and this was accompanied by significantly lower clinical remission rates at both short- and long-term follow-up. In CD, by contrast, persistence did not differ significantly from anti-TNF after another anti-TNF agent, and no significant differences in short- or long-term clinical effectiveness were observed between cohorts. The detrimental effect of a prior different MOA was therefore more consistent and extended to clinical effectiveness in UC, whereas in CD it was limited to a reduction in durability relative to first-line therapy. In CD, the cohorts were matched for disease behaviour and perianal history, and patients in whom anti-TNF was initiated for an active perianal indication were excluded; the observed differences are therefore unlikely to be explained by a higher prevalence of complex or perianal phenotypes. Residual confounding by unmeasured baseline severity (discussed below) is a more plausible contributor, particularly given the smaller size of the CD subgroup. Moreover, the absence of significant differences in adverse events or treatment discontinuation due to adverse events across

the three cohorts suggests that the observed differences in treatment durability are unlikely to be driven by safety concerns and instead reflect reduced clinical effectiveness.

The observational nature of our study does not allow us to provide a definitive mechanistic explanation for this phenomenon. Notably, the reduction in effectiveness and durability was not limited to comparisons with first-line anti-TNF therapy—which might be expected—but was also observed, particularly in UC, when compared with the use of a second anti-TNF agent following prior anti-TNF exposure. This finding is of particular interest, as both scenarios represent second-line therapy, with the key distinction being the MOA previously employed.

Experimental evidence has shown that exposure to anti-TNF therapy can induce expansion of TNFR2-positive T cells associated with the interleukin-23 receptor pathway [29, 30]. Conversely, it is conceivable that prior treatment with IL-12/23 inhibitors such as ustekinumab or with anti-integrin therapies such as vedolizumab may promote immune cell selection or pathway modulation that subsequently limits the effectiveness of anti-TNF agents [31]. While this hypothesis is biologically plausible, it remains speculative and warrants confirmation in dedicated translational and mechanistic studies.

Despite these findings, anti-TNF therapy retains a clear role after exposure to a different MOA in specific clinical situations. These include the emergence of perianal fistulizing CD, acute severe UC, and certain extraintestinal manifestations—particularly musculoskeletal involvement—as well as scenarios such as pregnancy, where anti-TNF agents have the most robust supporting evidence. In these settings, the reduced luminal durability observed in our study should be weighed against the specific benefits of TNF blockade rather than interpreted as a general contraindication to its use later in the treatment sequence.

This study has several important strengths. First, its nationwide multicentre design and overall sample size, together with

propensity-score matching, reduce the risk of selection bias and confounding. The exclusive use of data prospectively collected within a structured national registry, under standardized definitions, supports the consistency of the information analysed. Moreover, the use of propensity score matching allowed the construction of three well-balanced cohorts across all measurable baseline variables, minimizing confounding and reinforcing the robustness of the comparative analyses. This includes the drugs used, giving equal weight to the proportion of anti-TNF used in the three UC cohorts, which also accounts for a very low percentage of the total.

Nevertheless, several limitations should be acknowledged. Detailed information on baseline disease activity was not available, which may have introduced residual confounding related to disease severity. A further limitation concerns outcome assessment. Clinical response and remission were based on the responsible investigator's judgement rather than on systematically captured activity indices; the partial Mayo and Harvey-Bradshaw Index thresholds were applied as a reference framework but not necessarily computed prospectively at each visit. This may introduce assessment variability and a degree of subjectivity in the effectiveness outcomes, although it reflects routine real-world registry practice and applied equally across the three matched cohorts. Data on patient frailty and comorbidity burden were also lacking; however, the absence of significant differences in adverse events across cohorts suggests that major safety-related selection bias is unlikely. Another relevant limitation is that we do not know the pharmacokinetics of the failure of the first anti-TNF agent in the anti-TNF-anti-TNF cohort; however, the reasons for discontinuation of the first therapy (primary nonresponse, secondary loss of response, adverse events, etc.) followed a similar distribution in both groups. Although the overall cohort was large, the exposure subgroups—particularly patients with CD treated with anti-TNF after a different MOA ($n=66$)—were of modest size. The corresponding estimates, especially in CD, should therefore be interpreted with caution, and our findings would benefit from confirmation in larger dedicated cohorts. An important limitation is the exclusion of patients in whom anti-TNF therapy was initiated specifically for active perianal disease. This represents one of the most relevant clinical scenarios for anti-TNF use after exposure to a different MOA and one in which these agents have the strongest supporting evidence. While this exclusion was necessary to preserve a homogeneous, luminal-focused outcome assessment, it limits the generalisability of our findings to the perianal setting, which should be specifically addressed in future studies. Although ENEIDA applies standardized variable definitions and structured data-entry guidance to harmonize data collection across centres, it does not include a structured external monitoring or source-data verification process. As with any large real-world registry without external auditing, this entails a potential for inter-centre variability and data inaccuracies that cannot be entirely excluded. In addition, baseline corticosteroid exposure and objective measures of inflammatory burden, including CRP, faecal calprotectin, endoscopic activity and radiologic findings, were not consistently available across the registry and could therefore not be included in the propensity score model or used as longitudinal response markers. Consequently, residual confounding by baseline disease severity cannot be excluded, and the clinical effectiveness outcomes should be interpreted as

pragmatic, registry-based estimates rather than objective treatment-to-target endpoints.

In conclusion, this study provides the first real-world evidence on the use of anti-TNF therapy after failure of a biologic agent with a different MOA in IBD. Our findings demonstrate that the effectiveness of anti-TNF agents in this setting is significantly lower than when they are used as first-line therapy or even after prior exposure to another anti-TNF agent. These results suggest that not only the number of previous therapies, but also the specific mechanisms of action previously employed, may critically influence subsequent treatment response.

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Conflicts of Interest

M.B.A. has served as a speaker, consultant and advisory member for or has received research funding from MSD, AbbVie, Janssen, Kern Pharma, Takeda, Galapagos-Alpha Sigma, Pfizer, Sandoz, Fresenius, Avibax, Lilly, Biocon, Ferring, Faes Farma, Dr. Falk Pharma, Chiesi, Adacyte, TillotsPharma, OncoStellae and SunRock. J.P.G. 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/Alfasigma, Lilly, Sanofi, STADA, Teva, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillots Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Norgine, Italfarmaco and Vifor Pharma. F. Mesonero has served as a speaker for and received consulting fees from MSD, AbbVie, Takeda, Janssen, Pfizer, Ferring Pharmaceuticals, Kern Pharma, Dr. Falk Pharma, Galapagos, Alphasigma, Chiesi Farmaceutici, Tillots Pharma, Lilly and Faes Farma. E.D. has served as a speaker, or has received research or education funding or advisory fees from AbbVie, Adacyte Therapeutics, Alfasigma/Galapagos Biogen, Celltrion, Ferring, Gilead, GoodGut, Imidomics, Janssen, Kern Pharma, Lilly, MSD, Pfizer, Roche, Takeda, Tillots. Y.Z. has served as a speaker, or has received research or education funding or advisory fees from: AbbVie, Adacyte Therapeutics, Alfa-Sigma, Amgen, Boehringer Ingelheim, Dr. Falk Pharma, FAES Pharma, Fresenius Kabi, Ferring, Galapagos, Janssen-J&J, Kern Pharma, Lilly, MSD, Pfizer, Sanofi, Sandoz, Takeda, Tillots Pharma. C.M.P. has served as a speaker or has received research or education funding from Abbvie, Adacyte, Alfasigma, Chiesi, Faes, Ferring, Kern Pharma, Janssen, Lilly, Pfizer. E.I.F. has served as speaker, consultant and advisory member for or has received research funding from MSD, Abbvie, Takeda, Janssen, Galapagos/Alfasigma, Lilly, Dr. Falk Pharma, Pharma, Adacyte. I.V. has served as speaker, consultant and advisory member for and has received funding from MSD, Abbvie, Pfizer, Ferring, Shire Pharmaceuticals, Takeda, Tillots, Janssen, Galapagos and Lilly. Montserrat Rivero has served as a speaker or advisory member from Lilly, Takeda, Janssen, Abbvie, Galapagos, Ferring and Pfizer. E. Ricart has received support for congress and conference attendance, speaker fees, research support or consulting fees from MSD, Abbvie, Ferring, Janssen, Johnson&Johnson, Otsuka, Pfizer, Takeda, Faes Farma, Galapagos/Alphasigma, Kern Pharma, Lilly, Falk Pharma and Fresenius-Kabi. F. Bermejo has been a speaker, consultant and advisory member or has received research funding from Abbvie, Takeda, Janssen, Pfizer, MSD, Biogen, Amgen, Galapagos, Ferring, Faes Farma, Tillots Pharma, Chiesi, Vifor Pharma, Lilly. Á.P.-D. received financial support for travelling and educational activities from Johnson and Johnson, AbbVie, Takeda, Alfasigma, Lilly, Faes Farma and Ferring. Mercè Navarro-Llavat has served as a speaker or has received research or education funding from Abbvie, Janssen, Johnson & Johnson, Takeda, MSD, Pfizer, Ferring, Dr. Falk Pharma, Tillots Pharma, Chiesi, Faes Farma, Kern Pharma, Biogen, Galapagos, Alfasigma and Lilly. I.R.-L. has received financial support for travelling and educational activities from or has served as an advisory board member for Abbvie, Adacyte, Alfasigma, Biogen, Faes Farma, Ferring, Galapagos, Johnson&Johnson, Eli Lilly, Mirum Pharmaceuticals, Merck, Pfizer, Roche, Takeda and Tillots Pharma. Research support from AbbVie and Alfasigma. A.G.C. has received financial support for travelling and educational activities from or has served as an advisory board member for: AbbVie, Amgen, Celltrion, Lilly, Ferring, Galapagos, Fresenius Kabi, J & J, Pfizer, Sandoz, Takeda, Squibb, Bristol-Myers, Roche, Sandoz, Shire

and Merck. M.C. has served as a speaker or has received research or education funding or advisory fees from Takeda, Johnson and Johnson, Falk, Abbvie, Pfizer, Adacyte Therapeutics, Ferring, AlfaSigma, Gilead, Kern Pharma and MSD. D.M.R. has served as a speaker for and received consulting fees from AbbVie, Takeda, Janssen, Ferring, Tillots, Dr. Falk Pharma, Faes Farma and Persan. F. Bermejo has been a speaker, consultant and advisory member or has received research funding from Abbvie, Takeda, Janssen, Pfizer, MSD, Biogen, Amgen, Galapagos, Ferring, Faes Farma, Tillots Pharma, Chiesi, Vifor Pharma, Lilly.

Data Availability Statement

The data presented in this study are available on request to the corresponding author with prior authorization of our Ethical Committee, which can be obtained at [<https://www.iacs.es/investigacion/commit-e-de-etica-de-la-investigacion-de-aragon-ceica/>] accessed on 13 February 2026.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Covariate balance before and after propensity score matching. Standardized mean differences (SMD) for baseline covariates before (open blue circles) and after (filled green circles) matching, in Crohn's disease (A) and ulcerative colitis (B). Dashed line: SMD = 0.10 threshold for adequate balance. All covariates achieved adequate balance after matching, except age in ulcerative colitis, which showed a residual imbalance (SMD 0.20) despite substantial improvement from baseline (SMD 0.72), accounted for in the multivariable Cox model. CD, Crohn's disease; SMD, standardized mean difference; UC, ulcerative colitis.