













ORIGINAL ARTICLE

Frequency and Effectiveness of Dose Escalation and De-Escalation of Biologic Therapy in Inflammatory Bowel Disease: The RAINBOW-IBD Study of ENEIDA

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Received: 3 March 2025 | **Revised:** 9 April 2025 | **Accepted:** 21 July 2025

Handling Editor: Cynthia Seow

Funding: Eli Lilly and Company supported the statistical analysis, medical writing and publication fee of this study without being directly involved in any steps of its development (conception and design, analysis or interpretation of the results).

Keywords: biologics | dose escalation | inflammatory bowel disease

ABSTRACT

Background: Real-world data on dose escalation/de-escalation in inflammatory bowel disease (IBD) are scarce.

Aims: To assess the frequency, effectiveness and durability of escalation/de-escalation of infliximab, adalimumab, golimumab, vedolizumab and ustekinumab in IBD, and to identify factors influencing relapse and drug discontinuation and re-escalation efficacy.

Methods: We included patients from the ENEIDA registry of GETECCU who were exposed to biologics and analysed escalations/de-escalations. We assessed the impact of variables on durability, drug discontinuation and relapse after escalation/de-escalation.

Results: Of 19,720 patients on biologics, 5096 (26%) underwent dose escalation. Frequency of escalation per patient-year was 5% (infliximab), 7% (adalimumab), 7% (golimumab), 10% (vedolizumab) and 12% (ustekinumab). Clinical remission was recaptured in 32%–49% of patients. Durability of escalation (24 months) ranged from 66% to 88%. Drug discontinuation was associated with previous biologic exposure and disease duration (infliximab), monotherapy (adalimumab) and ulcerative colitis (ustekinumab). There were 669 de-escalations. The frequency per patient-year was 6%, 9%, 5%, 6% and 3% for infliximab, adalimumab,

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golimumab, vedolizumab and ustekinumab. Maintenance of remission after de-escalation was observed in 75%–100%. Durability of de-escalation (12 months) was 82%–90%. Factors associated with relapse were biologic exposure (infliximab) and age at de-escalation (adalimumab). Re-escalation benefited most patients.

Conclusions: In the long term, some patients with IBD need biologic escalation, which frequently recaptures durable clinical remission. De-escalation is feasible in some patients. Re-escalation is generally effective after relapse.

1 | Introduction

Inflammatory bowel diseases (IBD), encompass Crohn's disease (CD) and ulcerative colitis (UC). Over the past few decades, biologic drugs have emerged as a revolutionary therapeutic option for the treatment of IBD, transforming healthcare and significantly improving the quality of life of patients. Biologic agents, such as anti-tumour necrosis factor- α (TNF α) agents, vedolizumab (VEDO) and ustekinumab (UST) have proven their effectiveness in controlling intestinal inflammation [1].

However, approximately two-thirds of patients fail to achieve and maintain remission with these biological treatments, mainly due to non-response and loss of response (LOR) over time [1]. LOR to anti-TNF agents represents a therapeutic challenge to gastroenterologists, as these drugs are usually indicated in severe forms of the disease. In patients who experience LOR to a particular anti-TNF agent, dose escalation (either increasing the dose or decreasing the dosing intervals) is commonly used as a rescue strategy [2]. However, the frequency and effectiveness of dose escalation after LOR are barely known. Moreover, studies providing sufficient data to determine the incidence and effectiveness of dose escalation of other biologics such as VEDO or UST are also limited [3–5].

Although biologic dose escalation may be effective, it is associated with increased costs and potential safety concerns. Dose de-escalation is thus a logical option to discuss for selected patients in remission after dose escalation. However, de-escalation outcomes are scarcely known and this strategy may be associated with a high risk of relapse. Although this is a relevant decision in clinical practice, available data on anti-TNF dose de-escalation are currently lacking [6–10]. Moreover, although VEDO and UST may be key in the management of refractory IBD patients, data on de-escalation of these biologics are also very scarce [10, 11]. Finally, the effectiveness of dose re-escalation after prior dose de-escalation and subsequent IBD relapse is unknown.

For the above-mentioned reasons, our objective was to evaluate the frequency, persistence and effectiveness of dose escalation of biologic drugs (anti-TNF, VEDO and UST) in clinical practice. We also aimed to identify factors conditioning drug discontinuation after dose escalation. Finally, we aimed to describe the evolution after dose de-escalation, factors associated with relapse after dose de-escalation and effectiveness of re-escalation.

2 | Materials and Methods

2.1 | Study Design

We designed a multicentre, cross-sectional study selecting IBD patients included in ENEIDA registry who received biologic agents. ENEIDA registry is a prospectively maintained

nationwide database supported by the *Spanish Working Group on Crohn's Disease and Ulcerative Colitis* (GETECCU) [12]. Our study population comprised patients included in ENEIDA from January 1 2012 to December 28 2022.

2.2 | Ethical Considerations

ENEIDA registry was approved by the ethics committees of each participant centre. Informed consent was signed by all the participants before inclusion in the registry and each subject was issued with a personal code number to ensure that patient identity remains unknown. This study was conducted in accordance with the principles of the Declaration of Helsinki, the European General Data Protection Regulation (GDPR) 2016/679 and the Spanish Data Protection Organic Law 3/2018. The protocol was reviewed by the research committee of GETECCU before retrieval of the stored data from ENEIDA. The study was approved by GETECCU on December 19, 2022.

2.3 | Definitions

2.3.1 | Standard Doses

IFX: 5mg/kg every 8 weeks during the maintenance period; ADA: 40mg every other week during the maintenance period; GOL: 50mg monthly in patients whose weight is ≤ 80 kg, or 100mg in those whose weight is > 80 kg, during the maintenance period; VEDO: 300mg every 8 weeks during the maintenance period; and UST: 90mg every 8 or 12 weeks during the maintenance period.

2.3.2 | Dose Escalation

Dose escalation was defined as increasing the dose and/or decreasing the interval of administration from the previously described standard doses.

2.3.3 | Persistence of Dose Escalation/ Dose De-Escalation

Persistence is the duration of time over which patients remain in the escalated or de-escalated dosages.

2.3.4 | Dose De-Escalation

Dose de-escalation was defined as the reduction in the dosage and/or increase in the interval of administration from the dose of the escalation regimen.

2.3.5 | Response to Dose Escalation, Dose De-Escalation and Re-Escalation

Effectiveness of dose escalation, dose de-escalation and re-escalation was assessed based on the information included in ENEIDA according to clinicians' criteria: corticosteroid-free clinical remission, remission (with corticosteroids), response and non-response. Biomarkers, such as faecal calprotectin and endoscopic or radiological activity were not available.

2.3.6 | Relapse After Dose De-Escalation

Relapse was assessed based on the information available in ENEIDA according to clinician's criteria.

2.4 | Study Population

Adult patients with an established diagnosis of CD or UC who had been treated with biologic agents [infliximab (IFX), adalimumab (ADA), golimumab (GOL), VEDO or UST] for IBD were identified in ENEIDA. Out of these patients, those who had their treatment dose escalated (at least once) were specifically analysed. Patients who received the biologic drug for an indication different from IBD and patients with previous ileostomy or colostomy at the time of dose escalation were excluded. Patients were followed from the start date of the first dose escalation to the last visit or the end of follow-up, whichever came first.

2.5 | Data Collection

Demographic and clinical characteristics were obtained from ENEIDA registry, including disease location and behaviour, perianal disease and extraintestinal manifestations. IBD was categorised according to the Montreal classification [13]. For each biologic drug, the following variables recorded in ENEIDA were analysed: start date, type of drug, treatment indication, end date, reason for dose escalation, date of dose escalation, dose escalation regimen and response to dose escalation.

Data regarding de-escalation were also collected: date of dose de-escalation, dose de-escalation regimen, reasons for dose de-escalation and outcome after dose de-escalation [relapse of the disease, date of the relapse and response to a second dose escalation (re-escalation) of the treatment, when available]. Data regarding the re-escalation dosage, when available, were also included.

When a patient received more than one biologic with escalated dosage (including more than one anti-TNF), each treatment was assessed sequentially. Dose escalation, de-escalation and re-escalation events were analysed in the context of each treatment course, rather than as independent episodes. Therefore, patients were not counted multiple times in the analysis.

2.6 | Statistical Analysis

Categorical variables are expressed as number of events and percentage (with 95% confidence interval [CI]) and continuous

variables as arithmetic mean and the standard deviation (SD), or median and the interquartile range (IQR), depending on whether data were normally distributed or not. Categorical variables were compared using the chi-square test (χ^2) and quantitative variables using the appropriate test (Student's *t* or Wilcoxon) depending on whether their values followed a normal distribution.

The cumulative incidence of dose escalation and dose de-escalation was calculated and expressed as a percentage. The incidence rate per patient and year of follow-up was also estimated. The cumulative incidence of biologic discontinuation (after a dose escalation and dose de-escalation) and the cumulative incidence of relapse after them were assessed with the Kaplan–Meier method. The relapse rate of the patients who maintained the escalated doses during the follow-up was also analysed. Survival curves assessing the impact of several variables on the persistence of dose escalation and dose de-escalation, and on clinical relapse were compared using the log-rank test. To evaluate the persistence of each biologic drug, only those patients who achieved remission after dose escalation or dose de-escalation (maintained remission) were included. Cox regression models were performed to identify potential factors associated with therapy discontinuation and with the risk of relapse after dose escalation and dose de-escalation. The results were expressed as hazard ratios (HRs) with their corresponding 95% CI. The dependent variables used in the Cox regression models were discontinuation of the biologic drug (IFX, ADA, GOL, VEDO or UST) and relapse of IBD, respectively. The independent variables included in the multivariate analysis were: age at dose escalation/dose de-escalation, sex, IBD type, extraintestinal manifestations, IBD duration before the dose escalation, smoking history, concomitant therapy with immunosuppressants (at the time of dose escalation/dose de-escalation), and previous biologic exposure. Also, all the variables that reached statistical significance in the univariate analysis were included in the multivariate analysis. In the log-rank test and the multivariate analysis, *p*-values <0.05 were considered statistically significant.

3 | Results

3.1 | Study Population

A total of 19,720 patients under treatment with biological agents, from 72 Spanish centres, were registered in ENEIDA (approximately one-third of the centres contributing patients to this study were secondary-level hospitals). Of them, 5096 (26%) underwent dose escalation and were specifically analysed (CD = 3689 and UC = 1407). In total, biologic dose escalations were performed in 1904 patients treated with IFX, 2567 patients with ADA, 109 patients with GOL, 402 patients with VEDO and 621 patients with UST. Characteristics of the study population (dose-escalated patients) are detailed in Table 1.

A total of 669 (12%) dose de-escalations from previous dose escalations were performed: 232 (35%) for IFX, 375 (56%) for ADA, 9 (1%) for GOL, 27 (4%) for VEDO and 26 (4%) for UST (Table 2). The flow-chart of the study population is represented in Figure 1. A Sankey diagram of biologic treatment showing the flow of dose escalation, dose de-escalation and

re-escalation for the different biologic drugs is represented in Figure S1.

3.2 | Frequency, Effectiveness and Persistence of Biologic Dose Escalation

3.2.1 | Infliximab

Of the 1904 patients who underwent IFX dose escalation, 1137 (60%) were on a regimen of 10 mg/kg every 8 weeks. The cumulative incidence of IFX dose escalation was 15%, with a median time of follow-up of 24 months (IQR = 7–68). The incidence rate of dose escalation per patient-year of follow-up was 5% (95% CI = 4.3%–5.6%) (Figure 2a): 6% (95% CI = 5.4%–6.5%) in CD and 4% (95% CI = 3.9%–4.8% in UC). Frequency and effectiveness of biologic drugs dose escalation is summarised in Table 3a.

Out of 1904 IFX dose-escalated patients, 448 (24%) were biologic-experienced. Of them, after IFX dose escalation, 243 (54%) relapsed and IFX was withdrawn [80 (33%) within 1 year, 114 (47%) within 2 years, 141 (58%) within 3 years, 153 (63%) within 4 years and 165 (68%) within 5 years of follow-up]. Dose escalation was performed in 1456 (76%) IFX naïve patients. Of them, 796 (55%) patients relapsed and IFX therapy was discontinued in 239 (30%) within 1 year, 318 (40%) within 2 years, 382 (48%) within 3 years, 454 (57%) within 4 years and 494 (62%) within 5 years.

Among patients in remission after IFX dose escalation, the probability of maintaining the escalated dose at 12 and 24 months was 88% and 78%, respectively (Figure S2a).

Predictive factors of relapse and therapy discontinuation after IFX dose escalation are included in Table 4a.

3.2.2 | Adalimumab

Dose escalation was performed in 2567 patients treated with ADA. A 40 mg every-week dosage was used in 2054 (80%). The cumulative incidence of ADA dose escalation was 23% (2567/10,982). The incidence rate of dose escalation per patient-year of follow-up was 7% (95% CI = 6.3%–7.7%) (Figure 2b): 8% (95% CI = 7.2%–10.5%) in CD and 6% (95% CI = 5.5%–7.5% in UC). The frequency and effectiveness of ADA dose escalation are included in Table 3a. Out of the 2567 patients who underwent ADA dose escalation, 805 (31%) were biologic-experienced. Of them, after ADA dose escalation, 308 (38%) relapsed and ADA was withdrawn [12 (4%) within 1 year, 37 (12%) within 2 years, 59 (19%) within 3 years, 89 (29%) within 4 years and 123 (40%) within 5 years of follow-up]. ADA dose escalation was performed in 1762 (69%) naïve patients. Of them, 716 patients relapsed (41%) and ADA was stopped in 46 (6%) within 1 year, 107 (15%) within 2 years, 193 (27%) within 3 years, 301 (42%) within 4 years and 379 (53%) within 5 years.

Among patients in remission after ADA dose escalation, the probability of maintaining the escalated dose at 12 and 24 months was 82% and 71%, respectively (Figure S2b). Predictive factors of relapse and therapy discontinuation after ADA dose escalation were included in Table 4a.

3.2.3 | Golimumab

A total of 109/929 (12%) patients under treatment with GOL underwent dose escalation. The incidence rate of dose escalation per patient-year of follow-up was 7% (95% CI = 6.9%–7.1%) (Figure 2c): 3% (95% CI = 2.2%–5.5%) in CD and 11% (95% CI = 7.8%–12.3%) in UC. The frequency and effectiveness after GOL dose escalation are summarised in Table 3a. Among patients in remission after GOL dose escalation, the probability of maintaining the escalated dose at 12 and 24 months was 46% and 85%, respectively (Figure S2c). Fifty-seven (52%) of the 109 patients were biologic-experienced. Of them, 17 (30%) relapsed after dose escalation and GOL was withdrawn in: 7/17 (44%) within 1 year and 9/17 (55%) within 2 years of follow-up. GOL dose escalation was performed in 60 naïve patients. Of them, 20 (33%) patients relapsed and GOL was discontinued in: 8/20 (41%) within 1 year and 13/20 (64%) within 2 years. Due to the small sample size, it was not possible to perform a multivariate analysis to identify predictive factors of relapse and factors associated with therapy discontinuation after GOL dose escalation (Table 4a).

3.2.4 | Vedolizumab

Of the 2734 patients under treatment with VEDO, 402 (15%) underwent dose escalation with 300 mg every 4 weeks. The incidence rate of dose escalation per patient-year of follow-up was 10% (95% CI = 9.9%–10.1%) (Figure 2d): 9% (95% CI = 8.6%–10.5%) in CD and 11% (95% CI = 9.9%–13.1% in UC). The frequency and effectiveness of VEDO dose escalation is reported in Table 3a. Among patients in remission after VEDO dose escalation, the probability of maintaining the escalated dose at 12 and 24 months was 84% and 75%, respectively (Figure S2d). Predictive factors of relapse after VEDO dose escalation are included in Table 4a. Due to the small sample size, variables associated with the risk of therapy discontinuation after VEDO dose escalation could not be identified.

3.2.5 | Ustekinumab

In total, 621/3783 (16%) patients treated with UST underwent dose escalation. The incidence rate of dose escalation per patient-year of follow-up was 12% (95% CI = 11.9%–12.1%) (Figure 2e): 15% (95% CI = 13.4%–16.7%) in CD and 9% (95% CI = 7.7%–10.3% in UC). The frequency and effectiveness after UST dose escalation are included in Table 3a. Among patients in remission after UST dose escalation, the probability of maintaining the escalated dose at 12 and 24 months was 93% and 88%, respectively (Figure S2e). Predictive factors of relapse and therapy discontinuation after UST dose escalation are included in Table 4a.

3.3 | Biologic Dose De-Escalation

3.3.1 | Infliximab

A total of 232 (12%) IFX dose de-escalations from 1904 previous dose escalations were performed. The incidence rate of IFX dose de-escalation per patient-year of follow-up was 6% (95%

TABLE 1 | Characteristics of the study population with escalated doses.

	Infliximab (n = 1904)	Adalimumab (n = 2567)	Golimumab (n = 109)	Vedolizumab (n = 402)	Ustekinumab (n = 621)
Years, median (IQR)	43 (32–54)	42 (31–53)	45 (37–55)	45 (34–59)	45 (33–57)
Male sex, n (%)	1073 (56)	1347 (52)	44 (40)	206 (51)	321 (52)
Smoking, n (%)	638 (34)	1009 (40)	17 (16)	94 (24)	215 (35)
Family history of IBD, n (%)	298 (16)	400 (16)	13 (12)	61 (16)	97 (16)
EIMs, n (%)	607 (33)	887 (35)	25 (23)	122 (31)	209 (34)
IBD duration (years), median (IQR)	7 (3–14)	6 (2–14)	8 (3–14)	8 (4–15)	10 (5–18)
CD, n (%)	1274 (67)	2064 (81)	5 (5)	181 (45)	556 (90)
CD extent, n (%) ^a					
L1 ileal	402 (32)	747 (36)	1 (20)	53 (29)	210 (38)
L2 colonic	213 (17)	213 (10)	1 (20)	26 (14)	62 (11)
L3 ileocolonic	649 (51)	1084 (53)	3 (60)	102 (56)	288 (52)
L4 upper GI tract	303 (24)	504 (24)	1 (20)	47 (26)	161 (29)
CD behaviour, n (%) ^a					
B1 inflammatory	681 (53)	1122 (54)	2 (40)	91 (50)	291 (52)
B2 stricturing	394 (31)	710 (34)	3 (60)	75 (41)	209 (38)
B3 fistulizing	343 (27)	448 (22)	0 (0)	37 (20)	114 (21)
Perianal disease, n (%)	575 (45)	787 (38)	0 (0)	72 (40)	185 (33)
UC, n (%)	630 (33)	503 (19)	104 (95)	221 (55)	65 (10)
UC extent, n (%)					
E1 proctitis	21 (3)	20 (4)	1 (1)	5 (2)	1 (2)
E2 left-sided colitis	249 (40)	193 (38)	40 (38)	86 (38)	19 (29)
E3 extensive colitis	360 (57)	290 (58)	63 (61)	130 (58)	45 (69)
Concomitant treatment with immunomodulators, n (%)	1123 (59)	1105 (43)	49 (45)	140 (35)	188 (30)
Indication for dose escalation					
LOR, n/N (%)	891/1438 (62)	1427/2154 (66)	53/87 (61)	143/267 (54)	177/378 (47)
Partial response, n/N (%)	331/1438 (23)	599/2154 (28)	34/87 (39)	122/267 (45)	192/378 (50)
Previous biologic exposure, n (%)	448 (24)	805 (31)	57 (52)	366 (91)	587 (95)
Anti-TNF	441 (23)	800 (31)	57 (52)	366 (91)	576 (93)
1 anti-TNF	387 (20)	783 (30.4)	36 (33)	169 (42)	326 (53)
≥ 2 anti-TNF	54 (3)	17 (0.6)	21 (19)	197 (49)	250 (40)
Vedolizumab	25 (1.3)	24 (1)	2 (2)	—	139 (22)
Ustekinumab	26 (1.4)	21 (0.8)	1 (1)	61 (15)	—

(Continues)

TABLE 1 | (Continued)

	Infliximab (n = 1904)	Adalimumab (n = 2567)	Golimumab (n = 109)	Vedolizumab (n = 402)	Ustekinumab (n = 621)
Previous abdominal surgery, n (%)	450 (24)	615 (24)	5 (5)	83 (21)	18 (3)
1 surgery	245 (13)	373 (15)	1 (1)	45 (11)	8 (1)
≥ 2 surgeries	205 (11)	242 (9)	4 (4)	29 (7)	10 (2)

Abbreviations: CD, Crohn's disease; EIMs, extraintestinal manifestations; GI, gastrointestinal; IBD, inflammatory bowel disease; IQR, interquartile range; LOR, loss of response; TNF, tumour necrosis factor; UC, ulcerative colitis.

^aPatients could belong to more than one group.

CI = 5.8%–6.2%) (Figure 3a). The frequency and effectiveness of IFX dose de-escalation are summarised in Table 3b. Predictive factors of relapse after IFX dose de-escalation are included in Table 4b. The probability of maintaining the dose de-escalated at 12 months was 86% (Figure S3a). During the follow-up, 12 patients (5%) required IFX re-escalation, and response and remission were recaptured in 11/12 (92%) and 7/12 (58%) patients, respectively.

3.3.2 | Adalimumab

Overall, 375 (15%) ADA dose de-escalations from 2567 previous dose escalations were performed. The incidence rate of ADA dose de-escalation per patient-year of follow-up was 9% (95% CI = 7.4%–10.7%) (Figure 3b). The frequency and effectiveness of ADA dose de-escalation are summarised in Table 3b. Predictive factors of relapse after ADA dose de-escalation are included in Table 4b. The probability of maintaining the dose de-escalated at 12 months was 86% (Figure S3b). During the follow-up, 22 (6%) patients required ADA re-escalation. Of them, 13 (59%) regained remission and 22 (100%) patients showed response.

3.3.3 | Golimumab

Of the 109 patients on GOL dose escalation treatment, nine (8%) patients underwent dose de-escalation. The incidence rate of GOL dose de-escalation per patient-year of follow-up was 5% (95% CI = 1%–9%) (Figure 3c). The frequency and effectiveness of GOL dose de-escalation are reported in Table 3b. The probability of maintaining the dose de-escalated at 12 months was 88% (Figure S3c). During the follow-up, one re-escalation was performed leading to a response without remission. Predictive factors of relapse and therapy discontinuation could not be assessed due to the small sample size (Table 4b).

3.3.4 | Vedolizumab

A total of 27 (7%) dose de-escalations from 402 previous dose escalations were performed. The incidence rate of VEDO dose de-escalation per patient-year of follow-up was 6% (95% CI = 5.4%–6.6%) (Figure 3d). The frequency and effectiveness of VEDO dose de-escalation are summarised in Table 3b. The probability of maintaining the dose de-escalated at 12 months was 82% (Figure S3d). Due to the small sample size, predictive

factors of relapse and therapy discontinuation could not be identified (Table 4b). During the follow-up, two patients needed a re-escalation. Remission after re-escalation was achieved in both of them.

3.3.5 | Ustekinumab

Among the 621 patients with previous UST dose escalation, 26 (4%) underwent dose de-escalation. The incidence rate of UST dose de-escalation per patient-year of follow-up was 3% (95% CI = 2.9%–3.1%) (Figure 3e). The frequency and effectiveness of UST dose de-escalation are summarised in Table 3b. The probability of maintaining the dose de-escalated at 12 months was 90% (Figure S3e). Due to the small sample size, variables associated with the risk of relapse after dose de-escalation could not be identified (Table 4b). One patient (9%) relapsed after dose de-escalation and regained clinical remission after a re-escalation.

4 | Discussion

This is a multicentre study encompassing the largest real-world clinical practice cohort evaluating the frequency, persistence and effectiveness of dose escalation and dose de-escalation of biologics in IBD. Our results underline that dose escalation is required relatively frequently for all biologics in the long term, and it is an effective strategy in clinical practice, with a substantial response rate and a relatively high persistence over time. In a minority of patients, a dose de-escalation was performed, with a significant proportion of them maintaining their response during follow-up. Finally, in patients relapsing after dose de-escalation, re-escalation was generally effective.

There is a variable but relevant proportion of patients on long-term anti-TNF treatment who experience LOR [14]. Guberna et al. reported, in a recent meta-analysis, a 28% overall rate of anti-TNF dose escalation at a 1 year of follow-up in naïve and 39% in non-naïve patients, respectively [2]. The overall frequency of anti-TNF dose escalation was lower in our cohort, with a higher proportion of patients who underwent dose escalation in the first years after the start of the anti-TNF, which was later reduced in the long term (Figure 2). Thus, the relatively low incidence rate of dose escalation reported in our study is probably due to the long follow-up period of our cohort and a time-dependent pattern in which the need for dose escalation stabilises over time. Remission after biologic

TABLE 2 | Characteristics of the study population with de-escalated doses.

	Infliximab (n = 232)	Adalimumab (n = 375)	Golimumab (n = 9)	Vedolizumab (n = 27)	Ustekinumab (n = 26)
Years, median (IQR)	42 (31–55)	41 (31–51)	53 (35–61)	47 (42–61)	40 (28–49)
Male sex, n (%)	125 (54)	179 (48)	4 (44)	11 (41)	11 (42)
Smoking, n (%)	66 (29)	160 (43)	1 (11)	6 (22)	15 (58)
Family history of IBD, n (%)	38 (17)	60 (16)	1 (11)	8 (30)	2 (8)
EIMs, n (%)	74 (32)	140 (38)	1 (11)	7 (27)	7 (27)
IBD duration (years), median (IQR)	7 (4–15)	9 (5–16)	4 (3–14)	7 (4–11)	7 (4–13)
CD, n (%)	131 (57)	311 (83)	1 (11)	11 (41)	23 (89)
CD extent, n (%) ^a					
L1 ileal	35 (27)	83 (27)	0 (0)	2 (18)	11 (48)
L2 colonic	28 (21)	52 (17)	0 (0)	1 (9)	3 (13)
L3 ileocolonic	68 (52)	172 (55)	1 (11)	8 (72)	10 (44)
L4 upper GI tract	19 (15)	77 (25)	0 (0)	5 (45)	7 (30)
CD behaviour, n (%) ^a					
B1 inflammatory	72 (55)	175 (56)	1 (11)	4 (36)	13 (57)
B2 stricturing	32 (24)	108 (35)	0 (0)	7 (63)	8 (35)
B3 fistulizing	41 (31)	66 (21)	0 (0)	4 (36)	7 (30)
Perianal disease, n (%)	61 (47)	122 (39)	0 (0)	5 (45)	7 (30)
UC, n (%)	101 (43)	64 (17)	8 (89)	16 (59)	3 (11)
UC extent, n (%)					
E1 proctitis	4 (4)	1 (2)	0 (0)	0 (0)	0 (0)
E2 left-sided colitis	42 (42)	32 (50)	4 (50)	5 (31)	1 (33)
E3 extensive colitis	55 (54)	31 (48)	4 (50)	11 (69)	2 (67)
Concomitant treatment with immunomodulators, n (%)	146 (63)	159 (42)	4 (44)	9 (33)	9 (34)
Biologic exposure, n (%)	35 (15)	139 (37)	4 (44)	21 (78)	25 (96)
Anti-TNF	35 (15)	139 (37)	4 (44)	21 (78)	25 (96)
1 anti-TNF	28 (12)	138 (36)	2 (22)	12 (44)	16 (62)
≥ 2 anti-TNF	7 (3)	1 (1)	2 (22)	9 (34)	9 (34)
Vedolizumab	1 (0.5)	0 (0)	0 (0)	—	7 (27)
Ustekinumab	3 (2)	0 (0)	0 (0)	2 (9)	—
Previous abdominal surgery, n (%)	30 (13)	68 (18)	0 (0)	5 (19)	0 (0)
1 surgery	17 (7)	38 (10)		2 (7)	
≥ 2 surgeries	13 (6)	30 (8)		3 (12)	

Abbreviations: CD, Crohn's disease; EIMs, extraintestinal manifestations; GI, gastrointestinal; IBD, inflammatory bowel disease; IQR, interquartile range; TNF, tumour necrosis factor; UC, ulcerative colitis.

^aPatients could belong to more than one group.

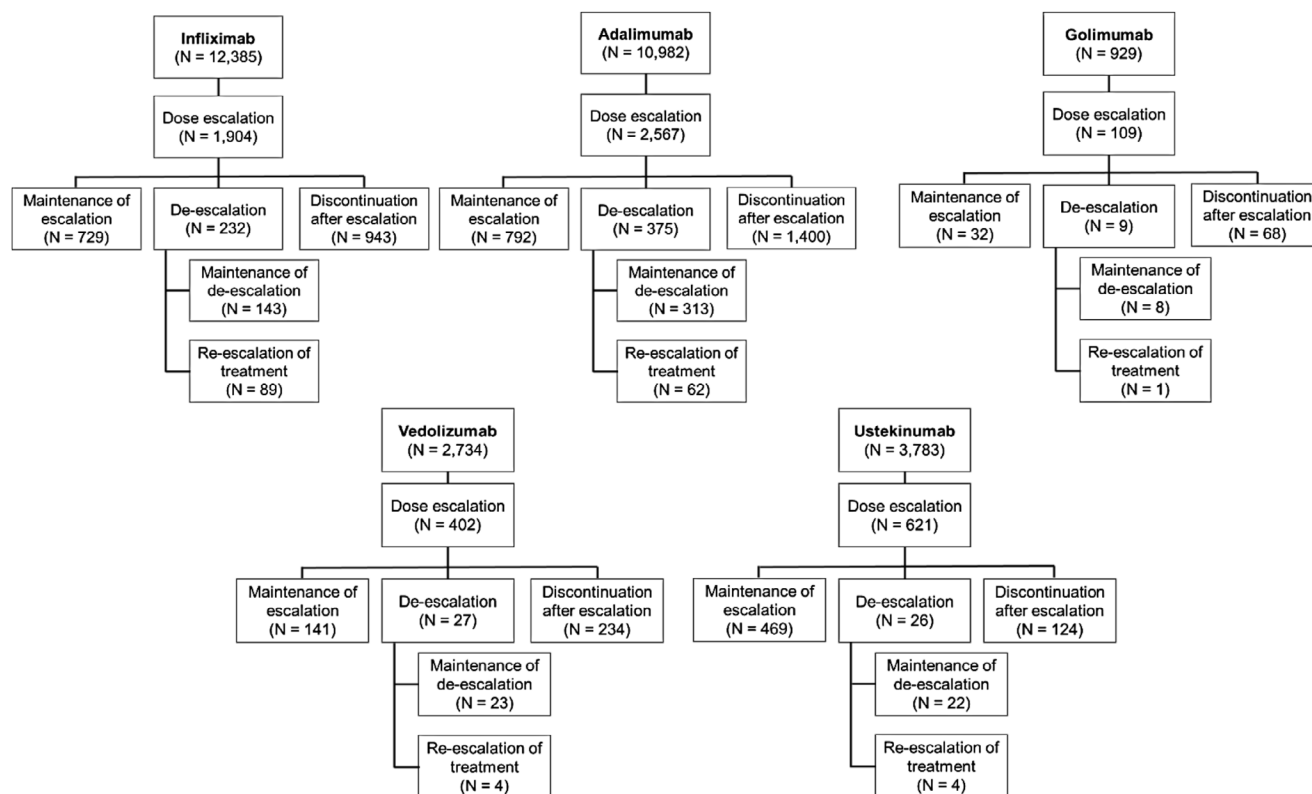


FIGURE 1 | Flow chart of the study population.

dose escalation was recaptured in about half of the patients. This finding is in accordance with previous studies [2].

Immunogenicity has been reported as one of the mechanisms of LOR to anti-TNF drugs [15]. Interestingly, the PANTS study showed that drug concentration at week 14 was the major independent risk factor associated with LOR or exit due to treatment failure [16]. With respect to anti-TNF persistence, they observed that those who had immune-mediated pharmacokinetic failure had the lowest rates of anti-TNF persistence [16]. Therapeutic drug monitoring (TDM) was not systematically performed in our cohort, and drug levels were not available in ENEIDA registry. The absence of concomitant immunosuppressants was the only factor associated with ADA dose escalation in our study. In contrast, the use of concomitant immunomodulators was not associated with lower rates of dose escalation in IFX-treated patients. Nevertheless, we observed that the risk of IFX dose escalation was higher in biologic-experienced than in biologic-naïve patients. This relevant finding is in accordance with previous reports [17].

Although VEDO is an effective therapy in IBD, some patients who initially respond subsequently experience secondary LOR [18, 19]. In our cohort, 15% of patients on VEDO underwent dose escalation, and a relevant proportion of them showed response and remission. In a systematic review and meta-analysis performed by Peyrin-Biroulet et al., the pooled incidence rates of LOR to VEDO were 48 and 40 per 100 person-years of follow-up in CD and UC, respectively [3]. Their results also supported that dose escalation may allow regaining response in over 50% of patients with LOR. Definitions of LOR to VEDO varied among the

studies included in the meta-analysis, which may explain the heterogeneity of results observed in these studies as well as in our own findings [20]. In our study, one of the factors associated with relapse after dose escalation was IBD duration, in accordance with a previous report [4].

In our cohort, UST dose escalation was performed in 16% of the patients, mainly due to LOR or partial response. This frequency was similar to those reported in other studies [21–24]. Although UST dose optimisation is common in clinical practice in patients with partial response or LOR, to date, the optimal management after this treatment change remains unclear. In our study, 47% of the patients achieved remission after UST dose escalation, with a UST persistence of 88% at 2 years. Similar remission rates have been recently reported [25]. Some factors associated with relapse after UST dose escalation have been identified, but only using univariate analysis [5, 26]. The high persistence of UST dose escalation is clinically relevant, due to the availability of its biosimilar version.

Dose de-escalation of biologic therapy offers an opportunity to minimise potential long-term adverse effects and reduce healthcare costs [27]. However, few studies have evaluated the safety and efficacy of dose de-escalation strategies, including dose reduction and extension of dosing intervals, with varying outcomes [28].

In our cohort, the frequency of anti-TNF dose de-escalation ranged from 8% to 15%. A recent review of 1474 patients described a weighted mean frequency of dose de-escalation (from a previous optimised dose) of 34%, with markedly

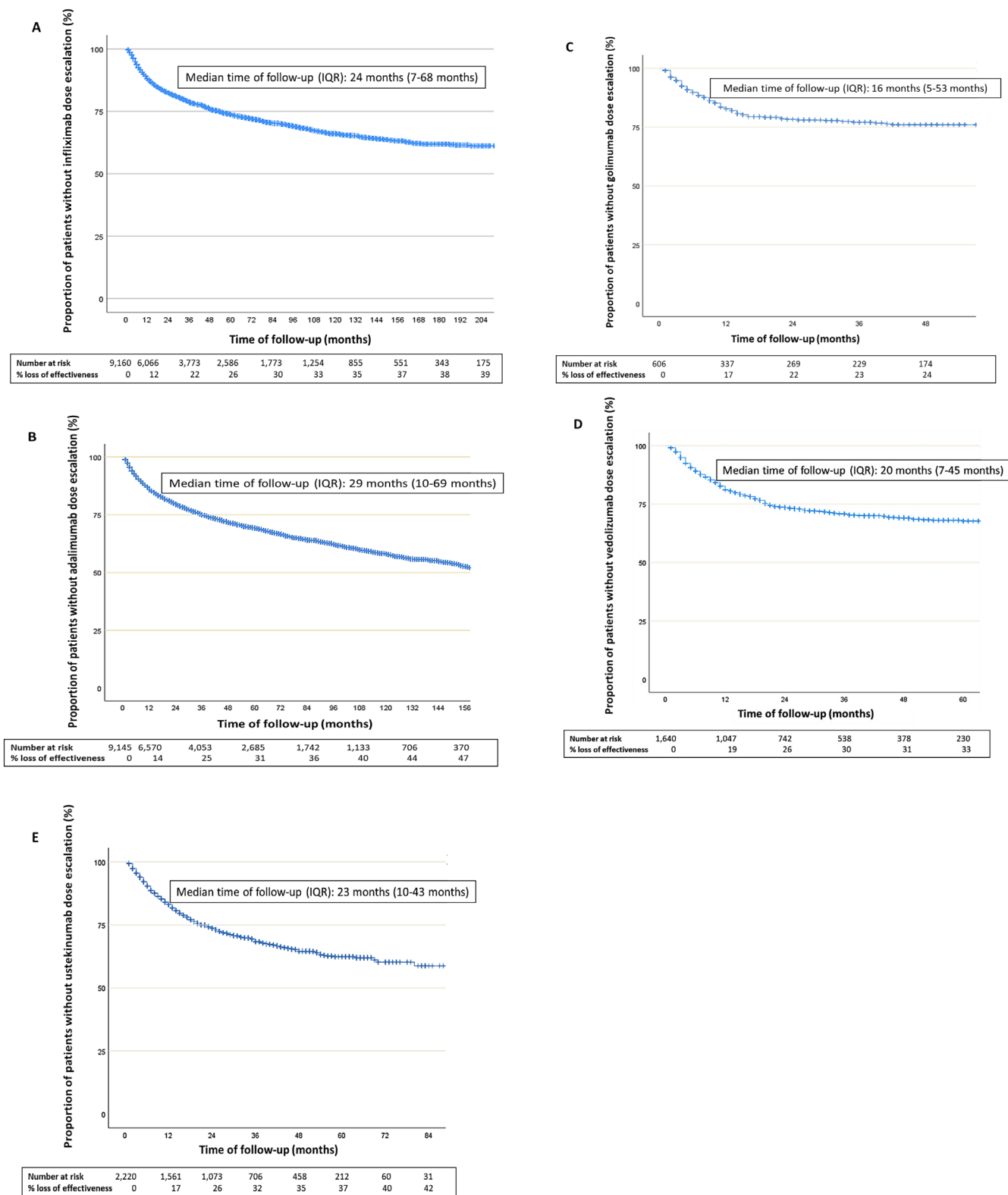


FIGURE 2 | Survival curves of loss of effectiveness in patients receiving biologics. (A) infliximab; (B) adalimumab; (C) golimumab; (D) vedolizumab; (E) ustekinumab. IQR, interquartile range.

heterogeneous results among studies, in which frequencies ranged from 6% to 71% [28]. Nevertheless, the mean frequency of dose de-escalation in our cohort was similar to that of other studies [28]. Despite its benefits for IBD treatment, anti-TNF dose de-escalation poses a risk of disease relapse. Thus, even

though the proportion of patients who relapsed after anti-TNF dose de-escalation in our cohort was relatively low, it is a non-negligible figure. Other studies have evaluated the relapse rate following anti-TNF dose de-escalation, which ranges from 10% to 41% [6, 7, 10, 29–33]. To guide dose de-escalation in

TABLE 3a | Frequency and effectiveness of biologic drugs dose escalation.

	Infliximab (N=1904)	Adalimumab (N=2567)	Golimumab (N=929)	Vedolizumab (N=2734)	Ustekinumab (N=3783)
Ulcerative colitis, <i>n/N'</i> (%) ^a	629/1407 (45)	500/1407 (36)	104/1407 (7)	22/1407 (16)	65/1407 (5)
Median time to dose escalation, months (IQR)	13 (6–35)	14 (6–38)	6 (3–12)	8 (4–16)	11 (4–16)
Reasons for dose escalation					
LOR, <i>n/N'</i> (%)	891/1438 (62)	1427/2154 (66)	53/87 (61)	143/267 (55)	177/378 (47)
Partial response, <i>n/N'</i> (%)	331/1438 (23)	599/2154 (28)	34/87 (39)	122/267 (45)	192/378 (50)
Low drug levels, <i>n/N'</i> (%)	216/1438 (15)	128/2154 (6)	—	—	9/378 (3)
Effectiveness of dose escalation					
Remission	471/965 (49)	549/1338 (41)	24/59 (41)	64/203 (32)	103/221 (47)
Response ^b	865/965 (89)	1157/1338 (86)	50/59 (86)	176/203 (87)	203/221 (92)

Abbreviations: IQR, interquartile range; LOR, loss of response.

^a*n*, number of dose escalated patients; *N'*, number of patients with ulcerative colitis on biologic treatment (infliximab, adalimumab, golimumab, vedolizumab or ustekinumab); *N*, number of patients on biologic treatment (infliximab, adalimumab, golimumab, vedolizumab or ustekinumab).

^bIncluding remission.

CD patients with anti-TNF therapy, TDM may be used [34]. Nevertheless, the precise way to use a proactive TDM strategy is not yet well established, and the minimal drug concentration required to consider dose de-escalation remains unknown [28, 35]. Concurrent immunomodulator use at the time of dose de-escalation varies among studies [7]. In our cohort, approximately 50% of the patients received immunomodulators at the time of dose de-escalation. However, the combination of both treatments –anti-TNF and immunomodulators– was not associated with lower relapse rates after dose de-escalation. On the other hand, previous biologic exposure was associated with relapse after anti-TNF dose de-escalation in our cohort. These results suggest a more refractory disease in biologic experienced patients, in whom dose de-escalation probably should not be considered.

To date, it seems clear that achieving deep (clinical, biological and endoscopic) remission decreases the risk of relapse after dose de-escalation [36]. Therefore, low faecal calprotectin and C-reactive protein levels, along with endoscopic remission, are key parameters to take into account before dose de-escalation in IBD [36–39]. In any case, our results show that for those who relapse after dose de-escalation, re-escalation of anti-TNF therapy appears to be generally effective, as supported by other studies^{25,38}. Nevertheless, the modest number of patients who underwent re-escalation in our study suggests that these findings should be interpreted with caution.

In our study, following VEDO dose escalation, dose de-escalation was performed in 7% of the patients. After VEDO dose de-escalation, 88% of the patients maintained remission and all of them maintained response. To date, the frequency of VEDO dose de-escalation has only been assessed in two studies, with prevalence rates of 15% and 1% [9, 40]. The outcomes after dose de-escalation in our cohort were in accordance with these

two studies. With respect to UST, in our study the frequency of dose de-escalation per patient-year of follow-up was 4% after a median time of 11 months. Three quarters of patients maintained remission after UST dose de-escalation, and the majority of them exhibited response. Two studies have evaluated the frequency of UST dose de-escalation, revealing a prevalence of 5% and 21% [33, 41]. The evidence on UST dose de-escalation outcomes is very scarce, likely because non-anti-TNF therapies are frequently prescribed as second or third-line options. Likewise, the frequency of VEDO and UST dose de-escalation was relatively low in our cohort, since these drugs were used mostly in refractory (biologic-experienced) cases.

Thus, based on our results, while dose de-escalation may be a viable option for some patients, it requires a cautious, individualised approach. The lack of clear predictive factors for relapse following de-escalation makes it challenging to choose when to apply this strategy. De-escalation should be instituted with caution (or not at all) in certain high-risk patient groups, such as those with previous biologic exposure as highlighted by our study, or those patients with perianal fistula or with multiple prior surgeries [28]. While several studies have demonstrated the potential benefits of TDM in optimising anti-TNF levels (mainly when supra-therapeutic trough concentrations are found) prior to deciding on dose de-escalation, the specific guidelines for implementing this proactive strategy are still not well defined. Therefore, careful patient selection, ideally based on clinical, biochemical and endoscopic remission, may maximise its success and minimise relapse rates after dose de-escalation.

Our study has some limitations inherent to its clinical practice design. First, we did not account for drug trough levels and anti-drug antibodies before dose escalation and dose de-escalation, which would have strengthened our results in terms

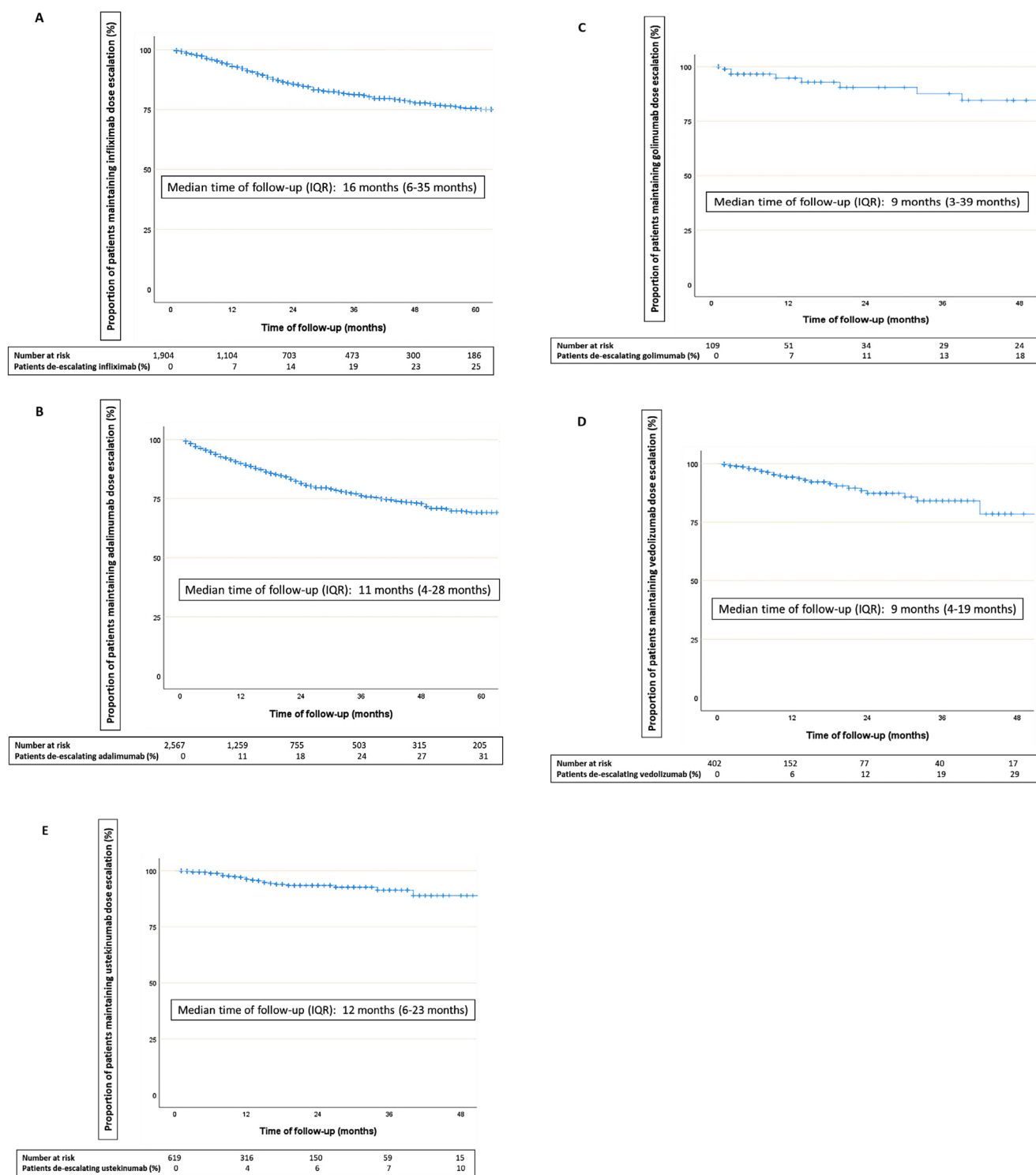


FIGURE 3 | Survival curves of dose de-escalation in patients with previous dose escalation. (A) infliximab; (B) adalimumab; (C) golimumab; (D) vedolizumab; (E) ustekinumab. IQR, interquartile range.

of treatment-related immunogenicity. However, treatment responses were based on physician assessment, which reflects real-world clinical practice. Second, due to the limited number of patients who received VEDO or UST dose de-escalation, definitive conclusions on these treatments could not be drawn. The modest sample size from VEDO and UST dose de-escalation precluded identifying risk factors for relapse and for therapy discontinuation. Finally, the response after dose escalation and

the outcomes after dose de-escalation were based on clinicians' criteria and endoscopic data were not available. Nevertheless, our study characterises the management of IBD patients in real clinical practice.

Our study has several strengths. It constitutes the largest cohort with the longest follow-up duration assessing the effectiveness of biologic drugs dose escalation and dose de-escalation. Our

TABLE 3b | Frequency and effectiveness of biologic drugs dose de-escalation.

	Infliximab (N=232)	Adalimumab (n=375)	Golimumab (n=9)	Vedolizumab (n=27)	Ustekinumab (n=26)
Median time to dose de-escalation, months (IQR)	15 (1–83)	12 (5–24)	14 (3–36)	11 (4–20)	11 (8–15)
Indication for dose de-escalation					
Clinical remission, <i>n</i> (%) ^a	216 (93)	334/375 (89)	9/9 (100)	26 (96)	26 (100)
Drug levels, <i>n</i> (%)	16 (7)	41/375 (11)	—	—	—
Evolution after dose de-escalation					
Maintained remission, <i>n</i> / <i>N'</i> (%)	106/132 (80)	157/209 (75)	5/5 (100)	14/16 (88)	9/12 (75)
Maintained clinical response, <i>n</i> / <i>N'</i> (%)	131/132 (99)	208/209 (98)	—	16/16 (100)	11/12 (91)
Relapsed, <i>n</i> / <i>N'</i> (%)	1/132 (1)	1/209 (1)	—	2/16 (12)	1/12 (9)

Abbreviation: IQR, interquartile range.

^aMaintained remission without corticosteroids and did not require dose re-escalation during the follow-up.**TABLE 4a** | Predictive factors of relapse and for therapy discontinuation after dose escalation.

Biologic drug	Factor	Hazard ratio	95% confidence interval
IBD Relapse			
Infliximab	Previous biologic exposure	1.2	1.1–1.4
	IBD duration	0.98	0.97–0.99
Adalimumab	Adalimumab monotherapy	1.2	1.01–1.35
Golimumab	—	—	—
Vedolizumab	Crohn's disease	1.56	1.1–2.2
Ustekinumab	Ulcerative colitis	2.4	1.5–3.9
Therapy discontinuation			
Infliximab	Previous biologic exposure	1.2	1.1–1.4
	IBD duration	0.98	0.97–0.99
Adalimumab	Adalimumab monotherapy	1.2	1.1–1.25
Golimumab	—	—	—
Vedolizumab	—	—	—
Ustekinumab	Ulcerative colitis	1.4	1.1–1.9

TABLE 4b | Predictive factors of relapse after dose de-escalation.

Biologic drug	Factor	Hazard ratio	95% confidence interval
Infliximab	Previous biologic exposure	2.7	1.1–6.9
Adalimumab	Age at dose de-escalation	1.08	1.02–1.15
Golimumab	—	—	—
Vedolizumab	—	—	—
Ustekinumab	—	—	—

study includes not only anti-TNF therapy but also VEDO and UST, for which previous experience regarding dose optimisation is scarce. Accordingly, we could assess the durability of biologic dose escalations and dose de-escalations. This nationwide cohort of IBD patients also identified predictive factors of non-response after dose escalation and risk factors for relapse after dose de-escalation, which can help make decisions in clinical practice, especially in refractory cases.

In conclusion, dose escalation and dose de-escalation of biologic therapies in IBD are critical components of a dynamic treatment paradigm aimed at optimising patient care. While dose escalation offers a clear benefit in cases of LOR, with a high proportion of patients achieving response (and remission) over time, dose de-escalation seems feasible for long-term management in selected patients, although it must be approached with caution. Future research should continue studying these strategies by exploring novel biomarkers to further enhance the precision

of therapeutic decisions for more effective and sustainable IBD management.

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Acknowledgements

ENEIDA Registry is supported by AbbVie, Lilly, Biogen, Galápagos, Pfizer and Takeda.

Conflicts of Interest

Cristina Rubín de Célix has received education funding from Ferring, Tillotts Pharma, AbbVie, Sandoz, Alfasigma, Lilly, Norgine, MSD, Pfizer, Takeda and Janssen; Elena Ricart has received support for congress and conference attendance, speaker fees, research support or consulting fees from MSD, AbbVie, Ferring, Janssen, Otsuka, Pfizer, Takeda, Faes Farma, Galapagos, Kern Pharma, Lilly and Fresenius-Kabi; Ruth de Francisco has received support for conference attendance, and research support from AbbVie, Faes Farma, Ferring, Janssen, Pfizer, Takeda and Galapagos; Francisco Javier García-Alonso has served as a speaker for Pfizer, Janssen and AbbVie, and has received research funding from Janssen and AbbVie; Fernando Gomollón has served as a speaker, consultant and advisory member for AbbVie and FAES-Farma. Fernando Gomollón has received research or education funding from: AbbVie, Janssen, Pfizer and Takeda; Laura Ramos has served as a speaker, consultant and advisory board member for MSD, Ferring, AbbVie, Pfizer, Adaclyte, Takeda and Janssen; Miriam Mañosa has served as a speaker, consultant and advisory member for or has received research funding from AbbVie, Galapagos, Janssen, MSD, Pfizer, Faes Farma, Takeda, Tillotts and Dr. Falk Pharma; Eva Iglesias has received financial support for travelling and educational activities from or has served as an advisory board member for AbbVie, Adaclyte, Janssen, Pfizer, Takeda and Falk; María José Casanova has received research or education funding from Pfizer, Takeda, Janssen, MSD, Ferring, AbbVie, Biogen, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi and Norgine; Antonio Giordano received travel grants from Janssen, Falk and Ferring; Mónica Sierra-Ausín has served as a speaker, or has received research or education funding from AbbVie, Pfizer, Takeda, Janssen, Galapagos, Ferring and Tillotts; Isabel Vera has served as a speaker, consultant and advisory member for and has received funding for: MSD, AbbVie, Pfizer, Ferring, Shire Pharmaceuticals, Takeda, Tillotts, Janssen and Galápagos; Rufo Lorente has served as a speaker, or has received research or education funding from AbbVie, Pfizer, Takeda, Janssen and Galapagos; Marta Piqueras has served as a speaker or has received research or education funding from Takeda, AbbVie, FAES Pharma, Galapagos and Janssen; Montserrat Rivero has served as a speaker or advisory member from AbbVie, Lilly, Takeda, Janssen, Galapagos, Ferring and Pfizer; Jordi Guardiola has served as a speaker, or has received research or education funding or advisory fees from Lilly, Roche, MSD, AbbVie, Celltrion, Kern Pharma, GoodGut, Takeda, Janssen, Pfizer, Galapagos, Sandoz, Bühlmann, Ferring and GE Healthcare; Iago Rodríguez-Lago has received financial support for travelling and educational activities from or has served as an advisory board member for AbbVie, Adaclyte, Alfasigma, Biogen, Celltrion, Chiesi, Faes Farma, Ferring, Fresenius Kabi, Galapagos, Janssen, Lilly, Mirum Pharmaceuticals, MSD, Pfizer, Roche, Takeda and Tillotts

Pharma. Research support from AbbVie. Iago Rodríguez-Lago is supported by a research grant from Gobierno Vasco-Eusko Jaurlaritz [Grant No 2020111061]; Ángel Ponferrada-Díaz has served as a speaker, a consultant or advisory member from AbbVie, Lilly, Takeda, Ferring, Alfasigma and Janssen; Carlos Taxonera has served as a speaker, consultant and advisory board member for MSD, AbbVie, Pfizer, Takeda, Galapagos, Fresenius Kabi, Lilly, Ferring, Faes Farma, Dr. Falk Pharma and Tillotts; Manuel Barreiro-De Acosta has received financial support for travelling and educational activities from or has served as an advisory board member for Pfizer, MSD, Takeda, AbbVie, Kern Pharma, Janssen, Fresenius Kabi, Biogen, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Chiesi, Gebro Pharma, Otsuka Pharmaceuticals and Tillotts Pharma; Jose M. Huguet has served as a speaker and consultant for or has received research funding from MSD, AbbVie, Takeda, Janssen, Pfizer, Ferring, Sandoz, Tillotts Pharma, Dr. Falk Pharma and Faes Farma; Cristina Rodríguez-Gutiérrez has served as a speaker, or has received research or education funding from AbbVie, Pfizer, MSD, Tillotts, Ferring, Lilly, Takeda, Janssen and Galapagos; Ramón Pajares has received financial support for travelling from Takeda; Teresa de Jesús Martínez-Pérez reports personal fees or non-financial support from AbbVie, Amgen, MSD, Janssen, Takeda, Pfizer, Chiesi, Tillotts Pharma, Kern Pharma, outside the submitted work; Pilar Nos has served as speaker, consultant and advisory board or has received research funding from MSD, AbbVie, Janssen, Takeda, Biogen, Lilly, Roche, Sandoz, Ferring, Adacety, Faes Farma, Kern Pharma, Pfizer, Vifor Pharma, Chiesi and Tillotts; Eugeni Domènech has served as a speaker, or has received research or education funding or advisory fees from AbbVie, Adacety Therapeutics, Biogen, Celltrion, Ferring, Galapagos, Gilead, GoodGut, Imidomics, Janssen, Kern Pharma, Lilly, MSD, Pfizer, Roche, Samsung, Takeda, Tillotts; María Chaparro has served as a speaker, consultant and advisory member for, or received research funding from, AbbVie, Celltrion, Chiesi, Faes Farma, Dr. Falk Pharma, Ferring, Gebro Pharma, Janssen, MSD, Otsuka Pharmaceuticals, Pfizer Inc., Roche, Shire Pharmaceuticals, Takeda, Tillotts Pharma and Lilly; Javier P. Gisbert 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. The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** apt70312-sup-0001-Supinfo01.docx.

Data S2: apt70312-sup-0002-Supinfo02.docx.