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An international multicentre study of SwiTching from Intravenous to subcutaneous inflixiMab and vEdolizumab in inflammatory bowel diseases: The TIME study

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Abstract

Background and Aims: Subcutaneous (SC) formulations of infliximab (IFX) and vedolizumab (VDZ) are approved for the treatment of inflammatory bowel diseases (IBDs). Our aim was to evaluate the effectiveness of switching from intravenous (IV) to SC formulations of IFX and VDZ in IBDs.

Methods: This multicentre, retrospective study collected data of adult patients with Crohn's disease (CD) or ulcerative colitis (UC) switched to SC IFX or VDZ. The primary endpoint was clinical remission at 12 months stratified based on timing of switch. A composite endpoint consisting of therapy discontinuation, reverse-switch, need for steroids, and drug optimization was evaluated. A multivariate analysis investigated the association between patients' characteristics and outcomes.

Results: Two hundred and thirty-one patients (59% UC, 53% male, mean age 44 ± 15 years, 68% IFX) from 13 centres were included. The switch occurred at Week 6 in a third of cases (36%). Median time to switch was 13 months. Most patients switched to SC IFX and VDZ were in clinical remission at 3 (87% and 77%), 6 (86% and 83%) and 12 (63% and 60%) months. In the multivariate analysis, there was no difference in clinical remission rate at 12 months; however, patients switched at Week 6 had a higher rate of experiencing any therapeutic

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changes at 3 (false discovery rate (FDR) = .002), 6 (FDR $<1\times10^{-10}$) or 12 months (FDR = .08). Clinical disease activity at baseline (only in UC) (FDR = .07) and previous exposure to biologics (FDR = .001) were risk factors for composite endpoint at 6 and 12 months.

Conclusion: SC IFX and VDZ are effective in daily clinical practice in IBD patients. Switching patients in remission reduces the risk of negative outcomes.

KEYWORDS

Crohn's disease, disease-based, inflammatory bowel disease, disease-based, Ulcerative colitis, disease-based

1 | INTRODUCTION

Infliximab (IFX) and vedolizumab (VDZ) are biological drugs approved worldwide for the management of patients with moderate-to-severe Crohn's disease (CD) and ulcerative colitis (UC).[1–4] Both IFX and VDZ are administered intravenously following an induction (infusions at Weeks 0, 2, and 6) and a maintenance phase.[5,6] Recently, new subcutaneous (SC) formulations of IFX and VDZ have been developed and approved. Randomized controlled trials investigated the pharmacokinetics, efficacy, safety and immunogenicity of SC IFX and VDZ in patients with inflammatory bowel disease (IBD).[7–9] SC drugs proved to be less immunogenic compared with the intravenous (IV) formulations and well tolerated by patients.[7,10] In patients initiating IFX or VDZ, the switch to SC formulations can be performed starting from Week 6, after two infusions (at Week 0 and Week 2). In those who are already in the maintenance phase with IV IFX or VDZ, the switch can be performed at any time based on the physician's choice. However, there is no commonly accepted strategy regarding the switch to SC drugs in clinical practice. To date, the optimal timing for switching patients from IV to SC drugs is not yet known. For this reason, we conducted a multicentre study to evaluate the effectiveness of switching from IV to SC formulations of IFX and VDZ in IBD in a real-life setting. We focused on the timing of the switch to define whether the early (at Week 6) or later (after Week 6) switch to SC drugs has an impact on patient outcomes.

2 | METHODS

2.1 | Study design, inclusion and exclusion criteria

This was an international, multicentre, retrospective cohort study. Thirteen European tertiary-level hospitals visiting over 1000 patients per year participated in the study. All consecutive adult patients with a confirmed diagnosis of IBD were eligible if they were on SC IFX or VDZ therapy and had at least 12 months of follow-up. Patients were required to have received IV induction therapy with IFX or VDZ (at least two infusions, at Week 0 and Week 2) and could be switched at Week 6 or later. The switch was defined as the transition from the IV to the SC drug. Paediatric patients (<18 years of age), those who had an uncertain diagnosis of IBD or a diagnosis of undetermined colitis, and those who were unable to understand or sign an informed consent form were excluded from the study. In addition, for each patient included in the study it was required to enrol one patient receiving IV medication prior to the approval of SC medications (control cohort) with a minimum follow-up of 12 months. These two populations were matched one-to-one for sex, age, disease and type of medication. Data from patients switched to SC at Week 6 were then compared with those of the control cohort to investigate any differences between the two groups.

2.2 | Study outcomes

The primary outcome of the study was to evaluate the rate of clinical remission at 12 months in IBD patients treated with SC formulations of IFX and VDZ comparing subjects who initiated SC medications at Week 6 or after Week 6. We also investigated the rate of persistence of SC medications (defined as the percentage of patients who continued therapy during follow-up), the occurrence of IBD-related hospitalization, IBD-related surgery, colorectal dysplasia/neoplasia, medical therapy escalation (defined as need for steroids, immunosuppressants, drug optimization or other therapeutic changes), and the rate of reverse switch to IV formulation. Moreover, a composite endpoint was assessed including rate of SC therapy discontinuation, reverse switch from SC to IV drug, need for steroids and drug

optimization. All these outcomes were assessed at 3, 6 and 12 months after the switch.

2.3 | Data collection

Patient data were collected by reviewing the medical reports of patients in the participating centres at the time of the switch to SC drug (baseline) and 3, 6 and 12 months after the switch. Similarly, in the control cohort, data were collected at the start of IV therapy and then at 3, 6 and 12 months. The following patient's characteristics, both for the study population and control group, were collected via an anonymized shared electronic case report form (CRF): age, sex, date of diagnosis, smoking history, location of disease, previous therapies for IBD, ongoing therapies for IBD, previous IBD-related surgery, family history of IBD, extraintestinal manifestations. We also evaluated drug dosage (if standard or increased), frequency of IV administration (every 4 or every 8 weeks) and timing of switch to SC drug (at Week 6 or > Week 6). For all patients, at each time point, clinical data were collected. Clinical remission was defined as Harvey Bradshaw Index (HBI) <5 for CD and partial Mayo score (pMS) <3 for UC (with no subscore >1). Furthermore, inflammatory biomarkers (C-reactive-protein (CRP) and faecal calprotectin), endoscopic procedures with histological reports and radiological/ultrasonographic data were reported, if available. Biochemical remission was defined as a faecal calprotectin ≤250 μg/g or CRP ≤5 mg/L. Endoscopic activity was assessed through the Simple endoscopic score for CD (SES-CD) ≥3 in CD (Rutgeert's score ≥2 in operated CD patients) and endoscopic Mayo score >1 in UC. Histological remission was defined as Nancy score ≤1 (only for UC). Radiological and ultrasound remission were defined as bowel wall thickness (BWT) ≤3 mm.

2.4 | Statistical analysis

The number of patients was established considering the available patients in all centres who were potentially eligible and fulfilled the inclusion and exclusion criteria. An IV reference group was included to allow for within-study exploratory comparisons of efficacy and safety end points between the SC drug group switched at week 6 and the IV group and descriptive comparisons between SC and IV formulations. Descriptive statistics of the baseline data were presented as means ± standard deviation (SD), medians and interquartile ranges (IQRs), or as percentages when appropriate. Differences in qualitative findings were tested using the χ^2 test using the ggstaplot R package.[11] The Wilcoxon test was used to compare differences in quantitative variables. Data carpentry and statistical multivariate analyses were conducted using the tidyverse and Hmisc R packages, respectively.[12,13] The dataset underwent meticulous preparation, cleaning, and transformation within the tidyverse framework to ensure data integrity. Four multivariate analyses were then performed patients switched to SC drug (1), comparison between SC group and IV control (2), comparison between SC group switched at Week 6 and IV control (3), and comparison between SC group switched after Week 6 and IV control (4) to identify any correlation between socio-demographic factors at baseline, treatment at baseline, disease features, clinical, biochemical, endoscopic activity of disease and incidence of negative outcomes in IBD patients: linear regression to examine relationships between continuous variables and logistic regression for categorical outcomes. Furthermore, to enhance the rigour of statistical inferences, *p*-values obtained analyses were subjected to correction using the false discovery rate (FDR) method to mitigate the risk of Type I errors associated with multiple hypothesis testing, maintaining a controlled balance between identifying true positives and minimizing the likelihood of false positives. Drug persistence probabilities were calculated by Kaplan–Meier statistics with survival and survminer R packages.[14,15]

2.5 | Ethical considerations

The study was performed according to Good Clinical Practice guidelines and was approved by San Raffaele Hospital Review Board. Data were collected in an anonymized way (clinical trial number: 37/INT//2023).

3 | RESULTS

3.1 | Population characteristics at baseline

In total, 231 patients (136 UC and 95 CD, 53% male, mean age 44 ± 15 years) were included in the analysis (Table 1). About two-thirds of patients were treated with IFX (158/231, 68%) while one-third was treated with VDZ (73/231, 32%). A limited proportion of patients were on concomitant therapy with steroids at baseline (13, 5.6%). A fifth of the subjects were on immunosuppressant therapy (52, 22.5%, of which 50 started combo therapy with IFX). The switch occurred at week 6 (after two infusions) in a limited proportion of cases (83/231, 36%). The median time to switch was 13 months (IQR 1–61). Most patients (186/231, 80.5%) were in clinical remission at the time of the switch.

TABLE 1 Baseline characteristics of patients ($n = 231$).

	All	Infliximab		Vedolizumab	
	231	Crohn's disease 76	Ulcerative colitis 82	Crohn's disease 19	Ulcerative colitis 54
Males	122 (52.8%)	41 (53.9%)	49 (59.8%)	4 (21.0%)	28 (51.8%)
Mean age (year) ± SD	43.9 ± 15.0	43.7 ± 15.2	43.8 ± 15.2	44 ± 14.6	44.3 ± 15.1
Disease duration (year) ± SD	12 ± 8.7	11.7 ± 8.8	11.7 ± 8.8	11.7 ± 8.4	11.8 ± 8.6
Disease location					
L1 ileal	39 (41.1%)	30 (39.4%)		9 (47.4%)	
L2 colonic	14 (14.7%)	13 (17.3%)		1 (5.2%)	
L3 ileo-colonic	42 (44.2%)	33 (42.7%)		9 (47.4%)	
Disease behaviour					
B1 inflammatory	44 (46.3%)	34 (44.7%)		10 (52.6%)	
B2 stricturing	33 (34.7%)	28 (36.9%)		5 (26.3%)	
B3 penetrating	18 (19.0%)	14 (18.4%)		4 (21.1%)	
Perianal disease	27 (28.4%)	22 (28.9%)		5 (26.3%)	
Disease extent					
E1 proctitis	32 (23.6%)		23 (28.0%)		9 (16.7%)
E2 left sided	52 (38.2%)		34 (41.5%)		18 (33.3%)
E3 pancolitis	52 (38.2%)		25 (30.5%)		27 (50.0%)
Previous surgery					
1 surgery	22 (9.5%)	15 (19.7%)	0 (0.0%)	7 (36.8%)	0 (0.0%)
>1 surgery	25 (10.8%)	18 (23.7%)	0 (0.0%)	7 (36.8%)	0 (0.0%)
Active Smokers	36 (15.6%)	18 (23.7%)	11 (13.4%)	3 (15.8%)	4 (7.4%)
EIMs	49 (21.2%)	19 (25.0%)	25 (30.5%)	1 (5.7%)	4 (7.4%)
Ankylosing spondylitis	5 (2.2%)	3 (3.9%)	2 (2.4%)	0 (0.0%)	0 (0.0%)
Erythema nodosum	9 (3.9%)	4 (5.3%)	4 (4.9%)	1 (5.7%)	0 (0.0%)
Psoriasis	4 (1.7%)	2 (2.6%)	2 (2.4%)	0 (0.0%)	0 (0.0%)
Previous use of biologics					
Never	138 (59.7%)	53 (69.7%)	58 (70.7%)	5 (26.4%)	22 (40.7%)
1 biologic	63 (27.3%)	16 (21.1%)	18 (22.0%)	7 (36.8%)	22 (40.7%)
>1 biologic	30 (13.0%)	7 (9.2%)	6 (7.3%)	7 (36.8%)	10 (18.6%)
Use of steroids					
Concomitant[a]	13 (5.6%)	0 (0.0%)	7 (8.5%)	1 (5.7%)	5 (9.2%)
Past	204 (88.3%)	59 (77.6%)	77 (93.9%)	15 (78.9%)	53 (98.1%)
Use of IMM					
Concomitant[a]	52 (22.5%)	16 (21,0%)	34 (41.5%)	1 (5.7%)	1 (1.8%)
Past	115 (49.8%)	51 (67.1%)	32 (39.0%)	12 (63.2%)	20 (37.0%)
Medications at baseline					
Duration of IV therapy in months (mean)	55.9	33.6	33.9	58.7	57.2
Standard dosage (e8w)	135 (58.4%)	52 (68.4%)	33 (40.2%)	15 (78.9%)	35 (64.8%)
Optimized dosage (e4w)	9 (3.9%)	3 (3.9%)	2 (2.4%)	2 (10.5%)	2 (3.7%)
Optimized dosage (increased dosage)	3 (1.3%)	2 (2.6%)	1 (1.2%)	0 (0.0%)	0 (0.0%)
HBI[a]					
<5	83 (87.4%)	66 (86.8%)		17 (89.5%)	
≥5	12 (12.6%)	10 (13.2%)		2 (10.5%)	

TABLE 1 (Continued)

	All	Infliximab		Vedolizumab	
	231	Crohn's disease 76	Ulcerative colitis 82	Crohn's disease 19	Ulcerative colitis 54
pMS[a]					
≤2	103/136 (75.7%)		56/82 (68.3%)		47/54 (87.0%)
≥3	33/136 (24.3%)		26/82 (31.7%)		7/54 (13.0%)
SES-CD[a]					
<3	22/50 (44.0%)	21/43 (48.8%)		1/7 (14.3%)	
≥3	28/50 (66.0%)	22/43 (51.2%)		6/7 (85.3%)	
Rutgeert's score[a]					
≤1	10/17 (58.8%)	8/13 (61.5%)		2/4 (50.0%)	
≥2	7/17 (41.2%)	5/13 (38.5%)		2/4 (50.0%)	
Mayo endoscopic score[a]					
=0	24/91 (26.4%)		9/58 (15.5%)		15/33 (45.4%)
≥1	67/91 (73.6%)		49/58 (84.5%)		18/33 (54.6%)
Nancy score[a]					
≤1	6/18 (33.3%)		4/16 (25.0%)		2/2 (100.0%)
≥2	12/18 (66.7%)		12/16 (75.0%)		0/2 (0.0%)

[a]At the time of the switch to subcutaneous drug.

Abbreviations: e4w, every 4 weeks; e8w, every 8 weeks; EIMs, extraintestinal manifestations; HBI, Harvey-Bradshaw index; IV, intravenous; pMS, partial Mayo score; SD, standard deviation; SES-CD, Simple endoscopic score for Crohn's disease; y, years.

3.2 | Effectiveness at 3 months

Most patients (193/231, 83.5%) switched to SC IFX (137/158, 86.7%) and VDZ (56/73, 76.7%) were in clinical remission. Faecal calprotectin and CRP measurements were available for 124 (53.7%) and 148 (64.1%) patients with a mean value of 350.2 ± 945.3 μg/g and 2.4 ± 6.4 mg/dL. respectively. Most patients had normal faecal calprotectin (97/124, 78.2%) or CRP (133/148, 89.9%). Only a limited percentage of patients were monitored by IUS (13/231, 5.6%), imaging (3/231, 1.3%) or endoscopy (6/231, 2.6%). Five patients (2.2%) discontinued therapy at 3 months due to loss of response (2 on IFX and 3 on VDZ). Two patients (0.9%) treated with SC VDZ reverse-switched to the IV formulation (one with drug optimization every 4 weeks and one with administrations every 8 weeks). Four subjects (1.7%) experienced SC drug optimization including one patient treated with SC VDZ at double dosage every other week and three patients treated with weekly SC VDZ. There was a need for steroids in one patient treated with IFX and in two patients treated with VDZ or IFX. respectively. No patient experienced dysplasia, neoplasia, IBD-related hospitalization, surgery or death.

3.3 | Effectiveness at 6 months

Most patients (192/226, 84.9%) treated with SC IFX (134/156, 85.9%) and VDZ (58/70, 82.9%) were in clinical remission. Faecal calprotectin and CRP measurements were collected for 65 (28.8%) and 160 (70.8%) patients with a mean value of 207.8 ± 383.0 μg/g and 3.3 ± 10.5 mg/dL. respectively. In most patients' normal faecal calprotectin (56/65, 86.1%) and CRP (137/160, 85.6%) levels were detected. Endoscopic evaluation was available for approximately a quarter of subjects (50, 22.1%). A total of 22 patients (44.0%) were in endoscopic remission (14 on IFX and 8 on VDZ). Only a limited percentage of patients were monitored by IUS (24, 10.6%) or imaging (4, 1.8%). Nine patients (9/226, 4.0%) discontinued therapy at 6 months due to loss of response (6 on IFX and 3 on VDZ). Ten patients (4.4%) were reverse-switched to the IV formulation every 8 weeks (1 patient on IFX) or every 4 weeks (5 on IFX and 4 on VDZ). Four subjects (1.8%) experienced SC drug optimization including one patient treated with SC VDZ at double dosage every other week and three patients treated with weekly (2 IFX and 1 VDZ). No patient required additional courses of steroids or immunosuppressants. No patient experienced dysplasia, neoplasia, IBD-related hospitalization, surgery or death.

3.4 | Effectiveness at 12 months

Most patients (134/217, 61.7%) treated with SC IFX (92/147, 62.6%) and VDZ (42/70, 60.0%) were in clinical remission. The majority of subjects continued therapy after 12 months of treatment and as highlighted by the Kaplan–Meier curves, no difference in terms of persistence was identified between patients switched at Week 6 and those switched after Week 6 in both the IFX and VDZ groups ($p = .076$ and $p = .11$, respectively) (Figures 1 and 2). Faecal calprotectin and CRP measurements were available for 119 (54.8%) and 127 (58.5%) patients with a mean value of 259.5 ± 689.0 μg/g and 3.2 ± 13.0 mg/dL. respectively. Most patients achieved faecal calprotectin (97/119, 81.5%) and CRP (109/127, 85.8%) normalization. A quarter of patients underwent endoscopic evaluation (58/231, 25.1%). A total of 26 subjects (44.8%) were in endoscopic remission (21 on IFX and 5 on VDZ). Only a limited percentage of patients were monitored by IUS (24/217, 11.1%) or imaging (10/217, 4.6%). Eighteen patients (18/217, 8.3%) discontinued therapy due to loss of response (14 on IFX and 4 on VDZ). Five patients (2.3%) underwent reverse-switch (3 on IFX and 2 on VDZ). Seven subjects (3.2%) experienced SC drug optimization including double dosage of SC drug every other week (1 IFX and 1 VDZ) and weekly administration of SC drug (4 IFX and 1 VDZ). Systemic steroids were required in five patients treated with IFX (2.3%), while immunosuppressants were added in only one patient treated with IFX (0.5%). Four subjects (1.8%) underwent IBD-related hospitalization (3 on IFX and 1 on VDZ). One patient (0.5%) treated with VDZ underwent proctocolectomy. No patient experienced dysplasia, neoplasia or death.

3.5 | Composite endpoint stratified based on switch time

At the end of follow-up, the composite endpoint occurred in 72 cases (31.2%), mostly in patients treated with IFX (47/72, 65.3%). When stratifying data by time of switch (Week 6 or > Week 6), a numerically greater proportion of patients treated with IFX and switched at Week 6 experienced the composite endpoint compared to patients switched later (30/47, 63.8% vs. 17/47, 36.2%) (Figure 3). Similarly, in patients treated with VDZ, those switched at Week 6 had a numerically higher percentage of achieving the composite endpoint compared to the control group (17/25, 68.0% vs. 8/25, 32.0%) (Figure 4).

3.6 | Predictors of outcomes based on the timing of switch

At the multivariate analysis, no difference was found in clinical remission rate at Month 12 according to different timing of switch (at Week 6 vs. after Week 6). Patients

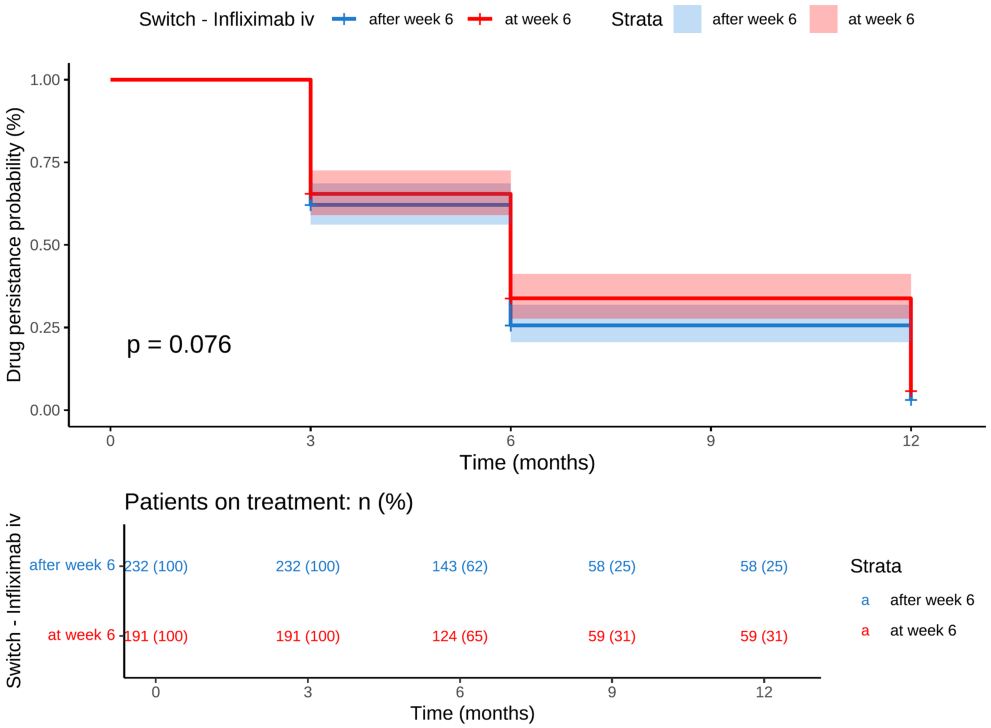

FIGURE 1 Kaplan–Meier curve showing the rate of drug persistence among patients treated with infliximab switched at Week 6 or after Week 6.

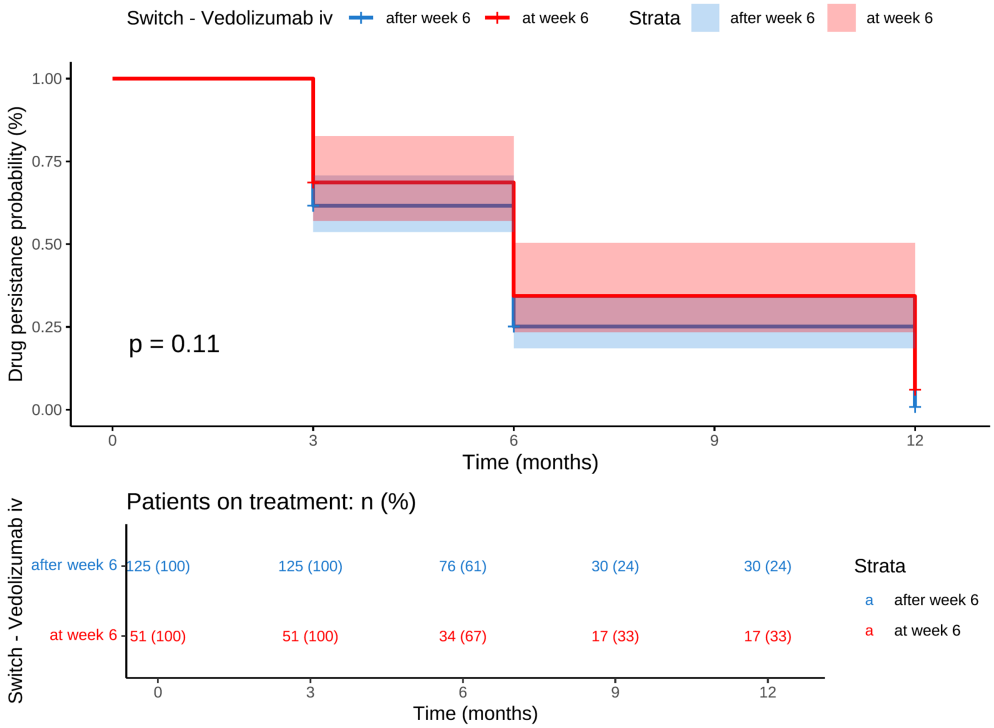

FIGURE 2 Kaplan–Meier curve showing the rate of drug persistence among patients treated with vedolizumab switched at Week 6 or after Week 6.

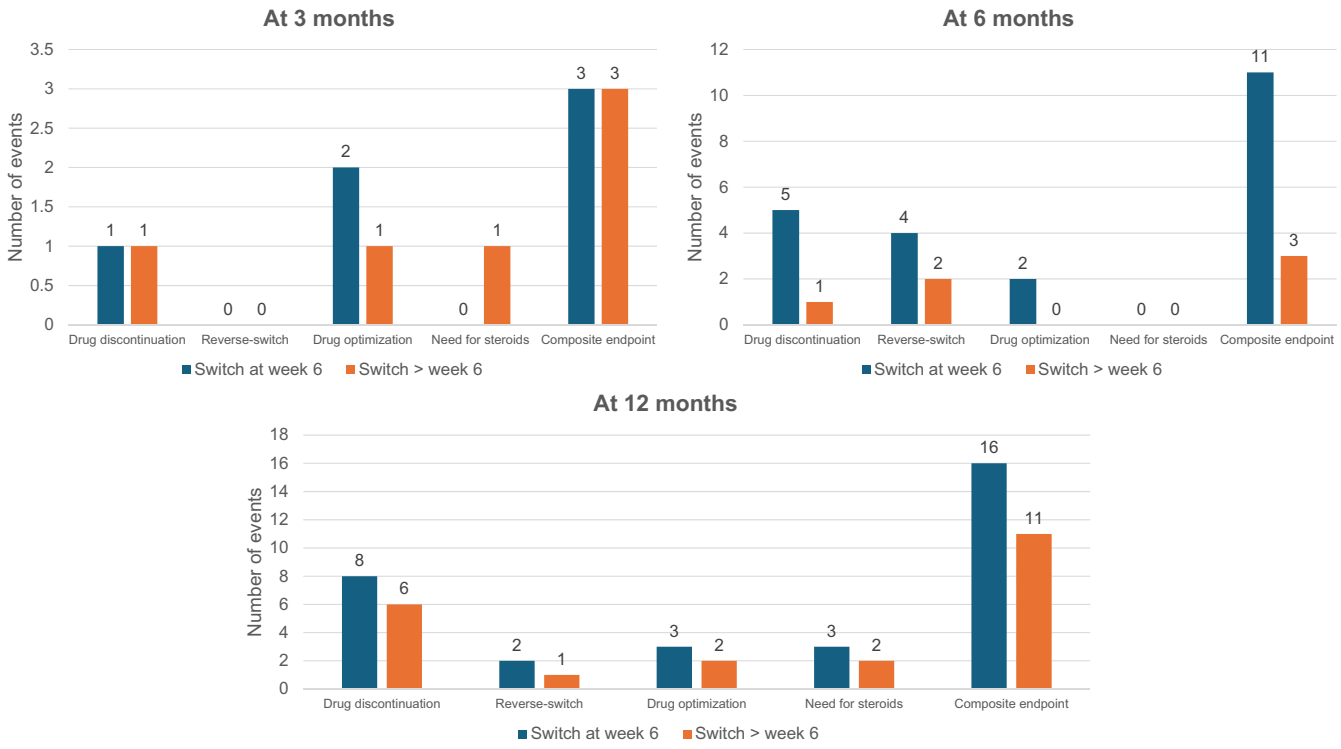

FIGURE 3 Composite endpoint at 3, 6 and 12 months in patients treated with infliximab.

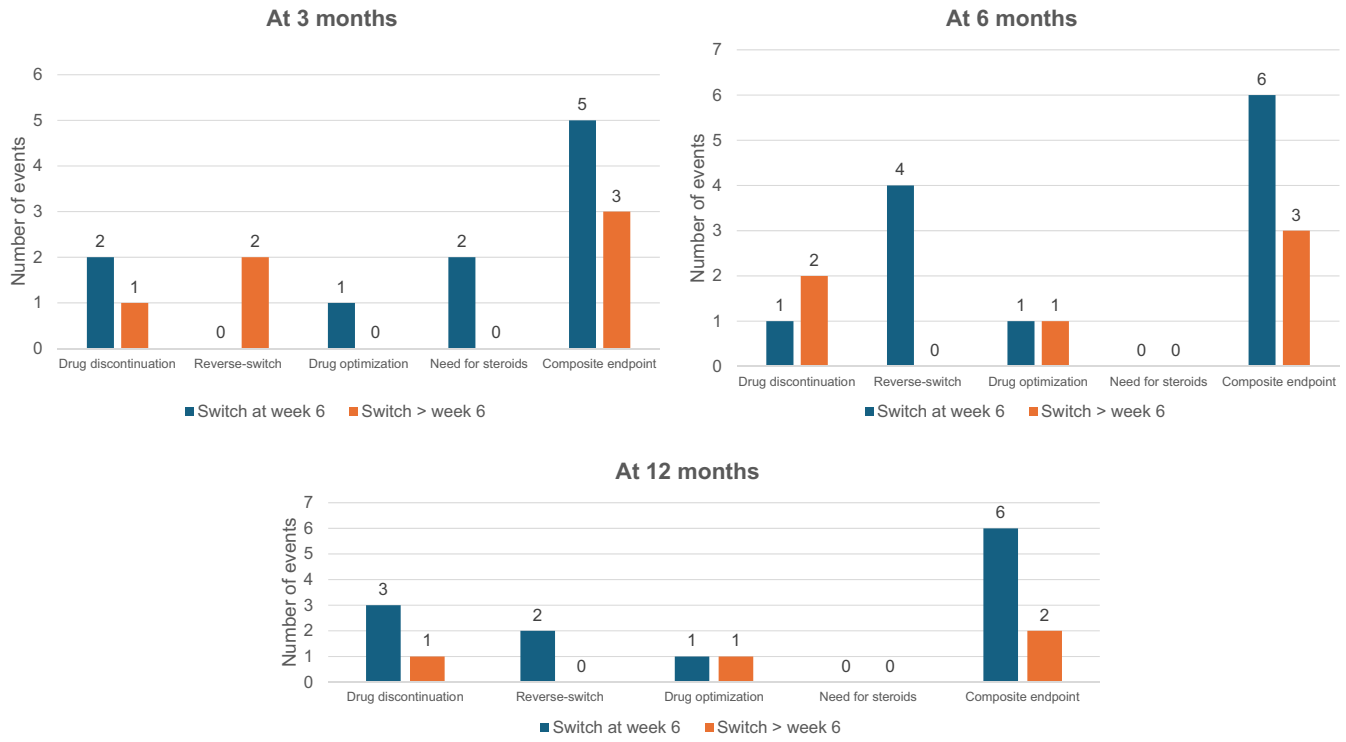

FIGURE 4 Composite endpoint at 3, 6 and 12 months in patients treated with vedolizumab.

switched at Week 6 had a higher rate of experiencing any therapeutic changes at 3 (FDR = 0.002, $p < .001$), 6 (FDR $<1\times10^{-10}$, $p < .001$) or 12 months (FDR = 0.08, $p = .008$) and clinical activity at 6 months in UC (FDR = 0.07, $p = .006$). Conversely, switch after Week 6 was associated with a higher rate of clinical remission at 6 months (FDR = 0.01, $p < .001$) and endoscopic remission at 12 months in CD (FDR = .006, $p < .001$). In addition, switch after Week 6 was inversely associated with the risk of experiencing the composite outcomes at 6 months (FDR = 0.08, $p = .008$). Clinical activity of disease at baseline (only in UC) (FDR = 0.07, $p = .006$) and previous exposure to biologics (FDR = 0.001, $p < .001$) were identified as risk factors for the composite endpoint at 6 and 12 months, respectively. In the multivariable analysis comparing the group switched to the SC drug at Week 6 and the IV control group, no difference was detected in terms of clinical remission, biochemical remission or endoscopic remission.

4 | DISCUSSION

This international multicentre study shows that SC formulations of IFX and VDZ are effective in the management of patients with IBD. Specifically, only a limited percentage of patients discontinued therapy (31/231, 12.8%) after 1 year of treatment. Furthermore, only a small proportion of patients experienced hospitalization, surgery, malignancy or required a reverse switch to IV medications. Our results are in line with the literature data confirming the effectiveness and the reliable drug persistence of SC formulations.[16–25] Of note, stratifying results by time of switch, a numerically greater percentage of patients switched early at Week 6 experienced hospitalization, surgery, need for steroids or medical therapy escalation. This suggests that timing of the switch could play a role in determining treatment effectiveness. Multivariate analysis revealed that patients switched at Week 6 had a higher rate of any therapeutic changes. Obviously, primary non-response is reported in up to 40% of patients with IBD, so this data must be carefully considered.[26] Moreover, comparing the data of patients switched to the SC drug at Week 6 with an IV control cohort, no difference in terms of clinical remission or endoscopic remission was found, supporting the use of SC drugs. Other observational studies have also compared the effectiveness of SC versus IV medications. A small prospective Korean study investigated differences between patients who were treated with IV IFX and patients in clinical remission who were switched to the SC drug.[27] No differences in terms of 1-year clinical remission, biochemical remission, and mucosal healing were found. Low drug concentrations (<3 μg/mL) were detected less frequently in patients treated with SC IFX compared to IV drug (0% vs. 43%, $p < .001$) highlighting an improved immunogenicity of the SC formulation. However, the time of the switch was not evaluated. A multicentre study from the United Kingdom compared drug persistence of IV and SC VDZ after one-year treatment

showing equivalent results (81.1% vs. 81.2%; $p=.98$).[21] However, patient selection bias could not be excluded as all patients were offered a switch to SC medication. Our study has a control cohort consisting of patients treated with IV drugs (matched with the SC cohort) before the arrival of SC drugs avoiding patient selection bias and supporting the use of SC drugs. SC formulations have several advantages over IV medications. In fact, they are easy to use, well tolerated by patients and are associated with a significant reduction in the indirect costs of the disease as they allow to reduce overcrowding in infusion rooms and reduce hospital admissions.[28–30] An Australian economic analysis of the financial impact of the transition from IV to SC IFX and VDZ estimated an increase in capacity of approximately 5256 h for the infusion centre, suggesting both substantial cost savings and a significant improvement in access to infusion centres.[31] However, there are no globally accepted recommendations regarding the optimal timing of the switch to SC medications. A recent Belgian expert consensus proposed to switch to SC formulations only CD patients experiencing both clinical and biochemical response or UC patients achieving clinical and endoscopic response.[32] Our study, for the first time, highlights how the time of the switch can have a role on the effectiveness of the drug. Patients who were switched without achieving clinical or endoscopic remission were less likely to have disease control. For this reason, it is legitimate to hypothesize that the switch to the SC drug should be proposed after at least clinical remission has been achieved. Our results reveal a discrepancy between clinical, endoscopic and histological activity at baseline. Although the rationale for this finding is not known yet, it has already been reported previously.[33,34] The strategy of switching patients to SC formulations has several practical implications. SC medication is the equivalent of IV medication every 8 weeks. Although there is evidence to support the optimization of SC formulations, in many countries this is not reimbursed thus preventing its wide use in clinical practice.[17] Therefore, switching to SC drug should be considered when the patient is in stable clinical remission and there is no need to escalate medical therapy. In case of disease recurrence after switch, an option may be the reverse switch to the IV drug. However, especially in patients treated with IFX, up to a quarter of patients experience an allergic reaction after reinduction, making this option less safe, especially if many months pass after the switch.[35] Infusion reactions after IV reinduction of VDZ are rare but there is still no robust evidence to support the efficacy of the reverse switch.[36]

To the best of our knowledge this is the first study to be specifically designed to evaluate the effectiveness of SC formulations of IFX and VDZ based on timing of the switch. Other strengths are the multicentre nature and the relevant sample size which provide reliability to the study. Furthermore, the presence of an IV control cohort allows the efficacy of the SC drug to be assessed and the risk of bias to be reduced. Finally, the outcomes assessed were measured using validated scores, strengthening the reproducibility of our data. However, there are also limitations that deserve to be mentioned. First, the retrospective design of the study. Second, given the purpose of the study, the safety profile of SC drugs, patient compliance and preferences towards SC formulations were not investigated. Literature data suggest that the body mass index (BMI) and in particular obesity can impact the effectiveness of SC drugs.[37] Unfortunately, given the retrospective study design it was not possible to calculate this data and evaluate any differences between the SC and IV formulations. Further prospective studies to address this issue are warranted. In addition, immunogenicity data such as serum drug concentrations and autoantibodies were not reported as they are not routinely performed in all the involved centres. A recent randomized clinical trial compared the pharmacokinetics, efficacy and immunogenicity of patients treated with SC IFX as monotherapy and those receiving combo therapy with SC IFX and immunosuppressants.[38] Interestingly, no difference was found between the two groups suggesting that in patients switched to the SC drug higher and more stable drug concentrations are achieved making combination therapy unnecessary. Another cross-sectional study investigated the effects of SC IFX concentrations on patient outcomes.[39] Interestingly, patients with higher drug concentrations were more likely to experience sustained clinical remission. A threshold concentration of 20 μg/mL was identified as the optimal SC-IFX concentration to predict deep remission (sensitivity: 0.91, specificity: 0.80, accuracy: 0.85).

Further large prospective studies are necessary to define whether the achievement of endoscopic, histologic (in UC) or transmural (in CD) remission before the switch to the SC drug could have a role in improving treatment persistence.

5 | CONCLUSION

The SC formulations of IFX and VDZ are effective for the treatment of patients with IBD. The optimal timing of the switch has not yet been identified. Achieving at least clinical remission before switching from IV to SC drug reduces the risk of drug discontinuation, optimization, need for steroids and reverse switch. Further studies to define the optimal timing to switch from IV to SC drugs are warranted.

AUTHOR CONTRIBUTIONS

F.D. and M.A. conceived the study. F.D. and G.P. wrote the manuscript and created tables and figures. L.M. performed the statistical analysis. A.D.B., R.G., A.A., B.C., L.P.-B., P.M., I.S., F.M., M.B., T.I., G.D., C.B., A.Z., F.F., S.S., M.C., J.P.G., M.J.G., G.M., N.V., G.J.M., P.E., F.U., S.D., G.F. and M.A. critically reviewed the content of the paper and discussed the statements. All authors approved and contributed to the final manuscript.

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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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REFERENCES

1. Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis*. 2020;14:4-22.
2. Raine T, Bonovas S, Burisch J, et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *J Crohns Colitis*. 2022;16:2-17.
3. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020;158:1450-1461.
4. Feuerstein JD, Ho EY, Shmidt E, et al. AGA clinical practice guidelines on the medical management of moderate to severe luminal and perianal fistulizing Crohn's disease. *Gastroenterology*. 2021;160:2496-2508.
5. Anon. Infliximab data sheet—Cerca con Google. Accessed December 17, 2023. https://www.google.it/search?q=infliximab+data+sheet&sca_esv=591624743&sxsrf=AM9HkKl59GSpVOrGMp4PJ2yt5TVof1cPVQ%3A1702804490026&ei=Crx-ZfSLAYmO9u8P0Jym6AQ&oq=infliximab+and+data+s&gs_lp=Egxnd3Mtd2l6LXNlcnAiFWluZmxpeGltYWIgYW5kIGRhdGEgcyoCCAEyBhAAGBYYHjIGEAAYFhgeMggQABgWGB4YD0jzU1D9N1iERHACeAGQAQCYAWagAZcGqgEDOS4xuAEByAEA-AEBwgIKEAAYRxjWBBiwA8ICChAAGIAEGBQYhwLCAgUQABiABMICCBAAGIAEGMsB4gMEGAAgQYgGAZAGCA&sclient=gws-wiz-serp
6. Anon. Vedolizumab data sheet—Cerca con Google. Accessed December 17, 2023. https://www.google.it/search?q=vedolizumab+data+sheet&sca_esv=591624743&sxsrf=AM9HkKlW3f-xJPdY_6ljnojqUvtllxV44w%3A1702804505083&ei=Gbx-ZcDOBPKE9u8P-OCjsAk&oq=veedolizumdata+sheet&gs_lp=Egxnd3Mtd2l6LXNlcnAiFHZlZWRvbGl6dW1kYXRhIHNoZWV0KgIIADIGEAAYHhgNMggQABgIGB4YDUjiI1DrBli_GHACeAGQAQCYAYEBoAHBCaoBAzYuNrgBAcgBAPgBAcICBBAAGEfCAgoQABhHGNYEGLADwgIGEAAYBxgewgINEAAYgAQYDRixAxixA8ICBxAAGIAEGA3CAggQIRigARjDBMICChAhGKABGMMEGAriAwQYACBBiAYBkAYF&sclient=gws-wiz-serp
7. Schreiber S, Ben-Horin S, Leszczyszyn J, et al. Randomized controlled trial: subcutaneous vs intravenous infliximab CT-P13 maintenance in inflammatory bowel disease. *Gastroenterology*. 2021;160:2340-2353.
8. Sandborn WJ, Baert F, Danese S, et al. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis. *Gastroenterology*. 2020;158:562-572.e12.
9. Vermeire S, D'Haens G, Baert F, et al. Efficacy and safety of subcutaneous vedolizumab in patients with moderately to severely active Crohn's disease: results from the VISIBLE 2 randomised trial. *J Crohns Colitis*. 2022;16:27-38.
10. Remy C, Caron B, Gouynou C, et al. Inflammatory bowel disease patients' acceptance for switching from intravenous infliximab or vedolizumab to subcutaneous formulation: the Nancy experience. *J Clin Med*. 2022;11:7296.
11. Patil I. Visualizations with statistical details: the "ggstatsplot" approach. *J Open Source Software*. 2021;6:3167.
12. Wickham H, Averick M, Bryan J, et al. Welcome to the tidyverse. *J Open Source Software*. 2019;4:1686.
13. Jr FEH, functions CD contributed several functions and maintains latex. Hmisc: Harrell miscellaneous. 2023 Accessed March 1, 2024. https://cran.r-project.org/web/packages/Hmisc/
14. Therneau TM. TL original S->R port and R maintainer until, Elizabeth a, et al. survival: survival analysis. 2009 Accessed March 11, 2024. https://cran.r-project.org/web/packages/survival/
15. Kassambara A, Kosinski M, Biecek P, et al. survminer: drawing survival curves using "ggplot2.". 2021 Accessed March 11, 2024. https://cran.r-project.org/web/packages/survminer/
16. Huguet JM, García-Lorenzo V, Martí L, et al. Subcutaneous infliximab [CT-P13], a true biologic 2.0. Real clinical practice multicentre study. *Biomedicine*. 2022;10:2130.
17. Buisson A, Nachury M, Reymond M, et al. Effectiveness of switching from intravenous to subcutaneous infliximab in patients with inflammatory bowel diseases: the REMSWITCH study. *Clin Gastroenterol Hepatol*. 2023;21:2338-2346. e3.
18. Smith PJ, Critchley L, Storey D, et al. Efficacy and safety of elective switching from intravenous to subcutaneous infliximab [CT-P13]: a multicentre cohort study. *J Crohns Colitis*. 2022;16:1436-1446.
19. Parisio L, Settanni CR, Varca S, et al. Effectiveness and safety of switching from intravenous to subcutaneous vedolizumab

formulation in inflammatory bowel disease patients in clinical remission. *J Gastrointestin Liver Dis*. 2023;32:452-459.
20. Kubesch A, Kruse N, Jungheim F, et al. Switching vedolizumab from IV to SC injection in inflammatory bowel disease patients with active disease: real-world experience from a German IBD cohort. *J Clin Med*. 2023;12:7657.
21. Lim SH, Gros B, Sharma E, et al. Safety, effectiveness, and treatment persistence of subcutaneous vedolizumab in IBD: a multicenter study from the United Kingdom. *Inflamm Bowel Dis*. 2023;izad166.
22. Ribaldone DG, Parisio L, Variola A, et al. Switching from VEDOlizumab intravenous to subcutaneous formulation in ulcerative colitis patients in clinical remission: the SVEDO study, an IG-IBD study. *Dig Liver Dis*. 2024;56:77-82.
23. Wiken TH, Høivik ML, Buer L, et al. Switching from intravenous to subcutaneous vedolizumab maintenance treatment in patients with inflammatory bowel disease followed by therapeutic drug monitoring. *Scand J Gastroenterol*. 2023;58:863-873.
24. Volkers A, Straatmijer T, Duijvestein M, et al. Real-world experience of switching from intravenous to subcutaneous vedolizumab maintenance treatment for inflammatory bowel diseases. *Aliment Pharmacol Ther*. 2022;56:1044-1054.
25. Buisson A, Nachury M, Bazoge M, et al. Long-term effectiveness and acceptability of switching from intravenous to subcutaneous infliximab in patients with inflammatory bowel disease treated with intensified doses: the REMSWITCH-LT study. *Aliment Pharmacol Ther*. 2024;59:526-534.
26. Marsal J, Barreiro-de Acosta M, Blumenstein I, Cappello M, Bazin T, Sebastian S. Management of non-response and loss of response to anti-tumor necrosis factor therapy in inflammatory bowel disease. *Front Med (Lausanne)*. 2022;9:897936.
27. Hong SN, Song JH, Kim SJ, et al. One-year clinical outcomes of subcutaneous infliximab maintenance therapy compared with intravenous infliximab maintenance therapy in patients with inflammatory bowel disease: a prospective cohort study. *Inflamm Bowel Dis*. 2023;30:izad094.
28. Harno-Tasihin J, Siregar L, Paajanen M, Arkkila P, Punkkinen J. Switching from intravenous to subcutaneous infliximab and vedolizumab in patients with inflammatory bowel disease: impact on trough levels, day hospital visits, and medical expenses. *Scand J Gastroenterol*. 2023;59:1-8.
29. Burdge G, Hardman A, Carbery I, Broglio G, Greer D, Selinger CP. Uptake of a switching program for patients receiving intravenous infliximab and vedolizumab to subcutaneous preparations. *J Clin Med*. 2022;11:5669.
30. D'Amico F, Solitano V, Aletaha D, et al. Biobetters in patients with immune-mediated inflammatory disorders: an international Delphi consensus. *Autoimmun Rev*. 2021;20:102849.
31. Hilley P, Wong D, Ma R, Peterson A, de Cruz P. Transitioning patients from intravenous to subcutaneous infliximab and vedolizumab for inflammatory bowel disease: what is the opportunity cost of improving access to healthcare? *Intern Med J*. 2024;54:970-979.
32. Fierens L, Liefferinckx C, Hoefkens E, et al. Introduction of subcutaneous infliximab CT-P13 and vedolizumab in clinical practice: a multi-stakeholder position statement highlighting the need for post-marketing studies. *J Crohns Colitis*. 2022;16:1059-1069.
33. Jharap B, Sandborn WJ, Reinisch W, et al. Randomised clinical study: discrepancies between patient-reported outcomes and endoscopic appearance in moderate to severe ulcerative colitis. *Aliment Pharmacol Ther*. 2015;42:1082-1092.
34. Colombel J-F, Keir ME, Scherl A, et al. Discrepancies between patient-reported outcomes, and endoscopic and histological appearance in UC. *Gut*. 2017;66:2063-2068.
35. Lichtenstein L, Ron Y, Kivity S, et al. Infliximab-related infusion reactions: systematic review. *J Crohns Colitis*. 2015;9:806-815.
36. Checkley A, Kristofek L, Bolgar W. P065 vedolizumab related infusion reactions in inflammatory bowel disease patients treated in an alternate care setting. *Gastroenterology*. 2019;156:S44-S45.
37. Admin S. European Crohn's and colitis organisation—ECCO—P591 negative impact of high body mass index on the efficacy of anti-TNFα agents in patients with inflammatory bowel disease. Accessed June 4, 2024. https://www.ecco-ibd.eu/publications/congress-abstracts/item/p591-negative-impact-of-high-body-mass-index-on-the-efficacy-of-anti-tnf-agents-in-patients-with-inflammatory-bowel-disease.html
38. D'Haens G, Reinisch W, Schreiber S, et al. Subcutaneous infliximab monotherapy versus combination therapy with immunosuppressants in inflammatory bowel disease: a post hoc analysis of a randomised clinical trial. *Clin Drug Investig*. 2023;43:277-288.
39. Roblin X, Nancey S, Papamichael K, et al. Higher serum infliximab concentrations following subcutaneous dosing are associated with deep remission in patients with inflammatory bowel disease. *J Crohns Colitis*. 2023;18:jjad188.

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