ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld-5084

Effectiveness and Safety of Switching from Intravenous to Subcutaneous Vedolizumab Formulation in Inflammatory Bowel Disease Patients in Clinical Remission

Laura Parisio[1], Carlo Romano Settanni[1], Simone Varca[1,2], Lucrezia Laterza[1], Loris Riccardo Lopetuso[1,3], Daniele Napolitano[1], Elisa Schiavoni[1], Laura Turchini[1], Caterina Fanali[1], Norma Alfieri[1], Marco Pizzoferrato[1], Alfredo Papa[1,2], Pia Clara Pafundi[4], Alessandro Armuzzi[5,6], Antonio Gasbarrini[1,2], Daniela Pugliese[1], Franco Scaldaferri[1,2], IBD UNIT-CEMAD

1) IBD UNIT – CEMAD (Centro malattie apparato digerente), Medicina Interna e Gastroenterologia, Fondazione Policlinico A. Gemelli IRCCS, Rome; 2) Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome; 3) Department of Medicine and Ageing Sciences, Center for Advanced Studies and Technology, Università degli Studi „G. D'Annunzio", Chieti-Pescara; 4) Epidemiology and Biostatistics Research Core Facility, Gemelli Science and Technology Park, Fondazione Policlinico Universitario Agostino Gemelli IRCSS, Rome; 5) IBD Center, IRCCS Humanitas Research Hospital, Rozzano, Milan; 6) Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy

Address for correspondence:
Franco Scaldaferri
IBD UNIT - CEMAD (Centro malattie apparato digerente), Medicina Interna e Gastroenterologia, Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy
franco.scaldaferri@policlinicogemelli.it

Received: 20.06.2023
Accepted: 21.08.2023

ABSTRACT

Background & Aims: Subcutaneous vedolizumab formulation has been shown to be as effective and safe as the intravenous one in randomized control trials. Real-life data are limited especially for patients receiving long-term intravenous therapy. This study aimed to evaluate the safety and effectiveness of switching from intravenous to subcutaneous vedolizumab in a large cohort of patients with stable clinical remission.
Methods: In this prospective cohort study, we enrolled consecutive patients attending our center between September 2021 and April 2022. The baseline demographic characteristics, 12- and 24-weeks follow-up clinical activity, C-reactive protein levels, and adverse events were recorded. The primary endpoint was to assess combined steroid-free clinical remission plus biochemical remission 24-week after the switch.
Results: 93 patients (43 Crohn's disease, 50 ulcerative colitis), switched to subcutaneous vedolizumab after a median duration of intravenous treatment of 36 months [IQR 16-52]. At baseline, 80 patients (86%) had a combined remission. At 24-week, 89.2% (n=74) maintained combined steroid-free clinical remission plus biochemical remission. 25 adverse events were reported, mostly SARS-CoV-2 infections and injection site reactions, with a further four recurrence episodes. Twelve patients (12.9%) discontinued subcutaneous administration and restarted intravenous vedolizumab.
Conclusions: Switching from intravenous to subcutaneous vedolizumab can be considered effective and safe for maintaining remission in patients with inflammatory bowel disease. In addition, this might reduce healthcare costs. However, large-scale real-life studies with long-term follow-up are necessary.

Key words: long-term – real-life – persistence – side effects – switching – vedolizumab – effectiveness.

Abbreviations: AE: adverse events; BR: biochemical remission; CD: Crohn's disease; HBI: Harvey Bradshaw Index; IBD: inflammatory bowel disease; IV: intravenous; MAbs: monoclonal antibodies; PMS: Partial Mayo Score; SC: subcutaneous; SFCR: steroid-free clinical remission; UC: ulcerative colitis; VDZ: vedolizumab.

INTRODUCTION

The management of inflammatory bowel disease (IBD) has been revolutionized by the advent of monoclonal antibodies (MAbs) [1]. Vedolizumab (VDZ) is a MAb-binding integrin α4β7 that blocks the interaction of the surface homing receptors of activated immune cells with the endothelium to interfere with lymphocyte diapedesis, thus resulting in gut-selective anti-inflammatory activity [1, 2].

Intravenous (IV) VDZ is used as either a first- or second-line biologic therapy for both induction and maintenance treatment in adults with moderately to severely active ulcerative colitis (UC) and Crohn's disease (CD) in cases of failure or contraindications to conventional or anti-TNFα therapy. Recently, subcutaneous (SC) formulation of VDZ has been marketed as a timesaving and home therapy option [3, 4]. In the VISIBLE I and II trials, patients received IV-VDZ 300 mg at weeks 0 and 2, and, in the case of clinical response, at week 6 randomized to either IV-VDZ 300 mg every 8 weeks or SC-VDZ 108 mg every 2 weeks or placebo. Subcutaneous VDZ 108 mg was shown to be equally effective and safe as IV-VDZ for both CD and UC patients [3, 5]. Real-world data published so far confirmed clinical effectiveness, remission rates, safety and quality-of-life scores maintenance [6, 7].

To date, no consensus exists on when IBD clinicians should consider switching from IV standard dosing to SC formulations for patients on long-term maintenance therapy in clinical practice [8].

In this view, the aim of this study was to evaluate the effectiveness and safety of switching from IV-VDZ to SC-VDZ in IBD patients in clinical remission and stable standard therapy with IV-VDZ in a real-life setting.

METHODS

Study Design and Sample

This is a prospective observational cohort study, enrolling consecutive patients affected by IBD on steroid-free clinical remission (SFCR) on IV-VDZ treatment for at least three months, at our IBD-Unit Center (CEMAD, Digestive Disease Center, Fondazione Policlinico Agostino Gemelli IRCCS of Rome, Italy) from September 2021 to April 2022, switched to SC-VDZ treatment. Steroid-free clinical remission was defined as clinical remission, meaning a Harvey Bradshaw Index (HBI) <5 for CD patients [9], or a Partial Mayo Score (PMS) <2 for UC patients [10], plus the absence of steroid therapy [11, 12]. All patients who were unable to comply with study procedures, those whose IBD treatment was expected to change during participation, as well as patients who either underwent colectomy or had stomas or were waiting for hospitalization or surgery were excluded from the study.

Ethical Considerations

This study was approved by our local Institutional Review Board (Fondazione Policlinico Universitario "A. Gemelli", March 31, 2022) and is in accordance with the 1975 Declaration of Helsinki and its later amendments. All patients signed a written informed consent form prior to enrolment in the study.

Data Collection

Upon enrolment, all demographic information and medical history was gathered, including type of disease, either CD or UC, date of diagnosis, Montreal classification [13], presence of extra-intestinal complications, smoking habit, previous and concomitant therapies, starting date, duration of IV-VDZ therapy and de-escalation.

After switching, the patients were followed-up for 24 weeks. Baseline, 12- and 24-weeks follow-up clinical activity, and C-reactive protein (CRP) levels were recorded. No fecal calprotectin (FCP) levels were collected, or endoscopy data. Clinical IBD activity, evaluated with HBI for CD [9] and PMS for UC [10], biochemical remission (BR) defined as CRP <5 mg/L, alongside with SFCR, were collected. Furthermore, the combined remission, defined as SFCR plus BR was collected at each timepoint, as well as overall follow-up period and persistence in therapy through-out the study observation period. We also registered all adverse events (AEs) occurred during the study period. The severity of AEs was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE – Version 5.0) [14].

Endpoints

The primary endpoint was to assess the combined SFCR plus BR, 24-weeks after switching from IV-VDZ to SC-VDZ.

As secondary endpoints, we further evaluated: 1) SFCR plus BR after 12-weeks after switching to SC-VDZ; 2) persistence on SC-VDZ therapy; and 3) potential factors affecting 24-weeks combined remission. Finally, we reported the safety outcomes, in terms of AEs that occurred throughout the study.

Statistical Analysis

Due to the explorative nature of the primary endpoint and real-life study design, no formal sample size calculation was needed.

The clinical and demographic characteristics of the entire sample are described using descriptive statistics. Qualitative variables were reported as absolute and relative percentage frequencies, while quantitative variables were reported as either mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. The Shapiro-Wilk test was applied to verify the Gaussian distribution of quantitative variables. Missing values (whether ≤15%) were treated by "*imputeR*" R package for multiple imputation using Lasso Regression methods centered on the mean for quantitative data, whilst classification trees for imputation by "rpartC" function, centered on the mode, were applied on qualitative data [15].

Between-group differences were analyzed using the Fisher exact test (with Freeman-Halton's extension, when needed) in the case of qualitative data, while quantitative variables were assessed using either the Student's t-test or the Wilcoxon-Mann-Whitney U test, as appropriate. Between-groups differences in age at enrolment, duration of disease and of IV-VDZ treatment were further represented by "violin plots", by using R packages "*ggplot2*", "*ggstatsplot*", "*ggpubr*", "*ggprism*" and "*ggsignif*" R packages, stratified for subsample [16-20].

Combined remission at 24 weeks will be calculated from the date of SC-VDZ treatment initiation through the last date of follow-up. Subjects who do not achieve "SFCR plus BR" at the last follow-up will be censored. The cumulative incidence of combined remission at 24 weeks was estimated using the Kaplan Meier (KM) method and later compared using the log-rank test. The KM curve has also been reported. The analysis will be performed with "*ggplot2*" and "*survminer*" R packages [16–21]. To assess the potential prognostic factors of complete remission (i.e., SFCR plus BR) at 24-weeks, Cox proportional hazards regression models were fitted, and hazard ratios (HR) and 95% confidence intervals (CI) were reported. The proportionality of the hazards was assessed through visual inspection of the hazards and Schoenfeld residuals. In cases of doubtful proportionality, Cox weighted regression models were fitted. „*survival*" and „*coxphw*" R packages were applied for the whole analysis [22-25].

Statistical significance was set at p-values < 0.05. Suggestive p-values ($0.05 \leq p < 0.10$) were further reported. All analyses were performed by R software version 4.2.0 (CRAN ®, R Core 2022, Vienna, Austria) [26].

RESULTS

Patients' Characteristics

Overall, 93 patients (43 with CD and 50 with UC) were enrolled in the study, with a median age of 53 years (IQR: 42–67 years). The median duration of disease was 11.5 years (IQR: 7–19)

and the median duration of IV-VDZ treatment was 36 months (IQR: 16–52). Smoking status was significantly associated with CD rather than UC. Of note, 50 of 93 patients (53.7%) were anti-TNFα exposed and 39 (41.9%) were naive to biologics and immunosuppressors. In depth, 41.9% (n=39) of patients were previously exposed to infliximab, 26.9% to adalimumab, 24.7% to azathioprine or 6-mercaptopurine, and 6.5% to golimumab, while only one patient had already been exposed to the first course of vedolizumab (1.1%) and two to ustekinumab (2.2%).

Most patients (94.6%) were on every 8-weeks maintenance therapy, whilst a 4-weeks interval between infusions was needed in 5.4% of the cases, without any statistical significance between the two diseases considered.

At baseline, all patients except for one were in SFCR and 80 (86%) patients had both SFCR plus BR (45 UC patients and 35 CD patients). All data are shown in Table I and Fig 1.

Effectiveness of Subcutaneous Administration

The combined remission observed in 86% of patients at baseline increased at week 24 to 89.2%. This trend was similar when focusing on CD and UC separately. The BR rate remained stable at 12 weeks but improved to over 90% at 24 weeks.

Table I. General characteristics of the study sample

	Overall (n=93)	Crohn's disease (n=43)	Ulcerative colitis (n=50)	p
Age (years)	53 (42-67)	56.0 (43.5-67.0)	51.0 (41.2-69.0)	0.784
Gender				1.000
Male	50 (53.8)	23 (53.5)	27 (54)	
Female	43 (46.2)	20 (46.5)	23 (46)	
Disease		-	-	n.a.
Crohn's disease	43 (46.2)			
Ulcerative colitis	50 (53.8)			
Duration of disease (years)	12 (7-19)	15 (7 - 22)	11 (7 - 17)	0.297
Smoking status	7 (7.5)	6 (14)	1 (2)	0.046
Extraintestinal manifestations	14 (15.1)	7 (16.3)	7 (14.0)	0.779
Disease localization				n.a
Ileal localization (L1)/Proctitis (E1)	13 (14)	12 (27.9)	1 (2)	
Colon localization (L2)/Left colitis (E2)	27 (29)	6 (14.0)	21 (42)	
Ileo-colon localization (L3)/Pancolitis (E3)	53 (57)	25 (58.1)	28 (56)	
Disease behavior				n.a.
Inflammatory behavior (B1)	20 (46.5)	20 (46.5)	-	
Stricturing behavior (B2)	17 (39.5)	17 (39.5)	-	
Penetrating behavior (B3)	6 (14.0)	6 (14.0)	-	
Therapy				
Prior treatment				
Naïve	39 (41.9)	18 (41.9)	21 (42)	1.000
Infliximab	39 (41.9)	16 (37.2)	23 (46.0)	0.409
Adalimumab	25 (26.9)	15 (34.9)	10 (20.0)	0.159
Golimumab	6 (6.5)	1 (2.3)	5 (10)	0.211
Vedolizumab	1 (1.1)	-	1 (2)	1.000
Ustekinumab	2 (2.2)	1 (2.3)	1 (2)	1.000
Tofacitinib	-	-	-	n.a.
Azathioprine/ 6-Mercaptopurine	23 (24.7)	11 (25.6)	12 (24.0)	1.000
Duration of IV-VDZ therapy (months)	36 (16 – 52)	46 (30 – 53)	29.0 (14.5 – 45.0)	0.010
IV-VDZ dose interval pre-switch				1.000
Every 8 weeks	88 (94.6)	41 (95.3)	47 (94.0)	
Every 4 weeks	5 (5.4)	2 (4.7)	3 (6)	
De-escalation of IV-VDZ	12 (12.9)	4 (9.3)	8 (16)	0.373

IV: intravenous; VDZ: vedolizumab. Qualitative data are expressed as absolute and relative percentage frequency, whilst quantitative as either mean and standard deviation (SD) or median and interquartile range (IQR). P-values were computed with either Chi-squared or Fisher-Freeman-Halton's exact test for qualitative data. Student's t test or Mann-Withney U test for independent samples were instead applied for quantitative variables. In bold significant findings ($p<0.05$).

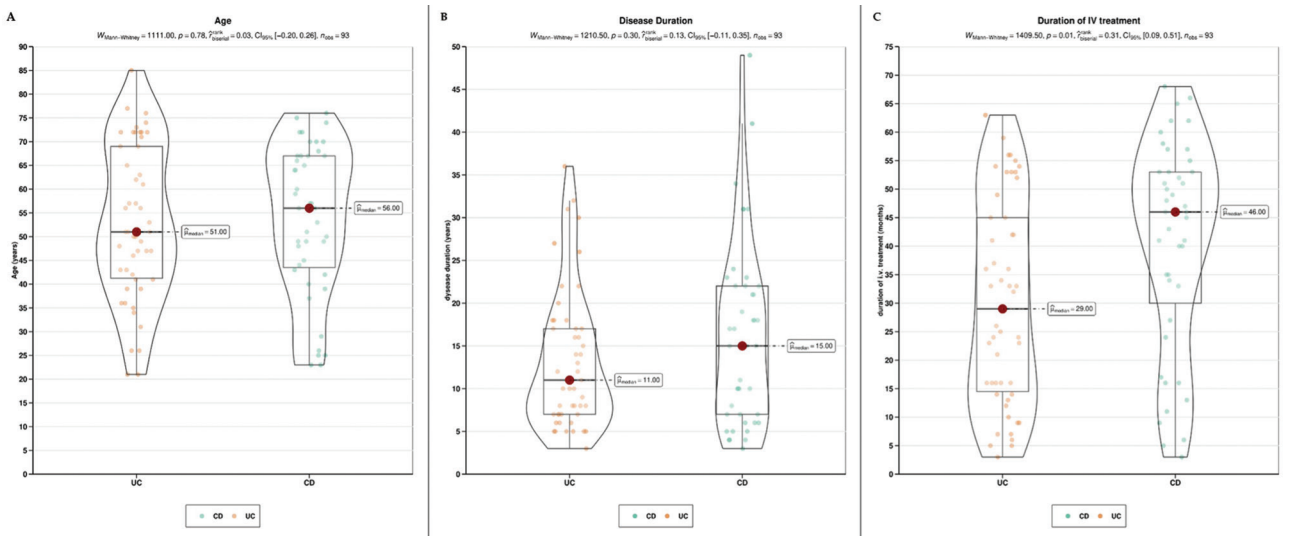

Fig. 1. Violin plot showing age (panel A), duration of disease (panel B), and duration of IV treatment (panel C) comparison between Crohn's disease (CD) and ulcerative colitis (UC).

Conversely, SFCR was almost complete (92 out of 93 cases) at baseline, and then slightly decreased over time (96.8% at 12-weeks and 97.8% at 24 weeks).

We further analyzed BR, SFCR and combined remission changes over time, both overall and stratified by CD and UC. When considering BR alone, no changes were observed either at week 12 or 24 compared with baseline, either overall or in the CD and UC subgroups. A similar trend was observed for SFCR.

Focusing more on combined remission, overall, of the 83 patients in SFCR plus BR at the 24-weeks follow-up, 74 (89.2%) were already in combined remission at baseline, while 9 (10.8%) displaying CRP levels at baseline >5 mg/L, did not meet the criteria for BR. All patients achieved combined remission during the 24-weeks follow-up period. Conversely, six patients lost SFCR plus BR from baseline, and four remained nonresponsive over time. There was no significant difference observed over time (Mc Nemar test p=0.606). Data are reported in Table II and showed in Fig 2.

Table II. Outcomes at baseline, 12- and 24-weeks since start of subcutaneous administration, both overall and stratified for disease

	Overall (n=93)	Crohn's disease (n=43)	Ulcerative colitis (n=50)	p
Baseline Outcome				
BR	81 (87.1)	36 (83.7)	45 (90)	0.537
SFCR	92 (98.9)	42 (97.7)	50 (100)	0.462
SFCR + BR	80 (86)	35 (81.4)	45 (90)	0.250
12w-Outcome				
BR	81 (87.1)	37 (86)	44 (88)	1.000
SFCR	90 (96.8)	42 (97.7)	48 (96)	1.000
SFCR + BR	78 (83.9)	36 (83.7)	42 (84)	1.000
24w-Outcome				
BR	85 (91.4)	37 (86)	48 (96)	0.138
SFCR	91 (97.8)	43 (100)	48 (96)	0.497
SFCR + BR	83 (89.2)	37 (86)	46 (92)	0.505

BR: biochemical remission; SFCR: steroid-free clinical remission. Qualitative data are expressed as absolute and relative percentage frequency and p-values computed with either Chi-squared or Fisher-Freeman-Halton's exact test.

Potential Predictors of Combined Remission at 24 Weeks

Cox proportional hazards regression models showed that patients with UC had a 2.2-time higher probability of undergoing combined remission at 24 weeks (HR=2.21, 95%CI: 1.39-3.51; p=0.001) (Table III).

Of note, in terms of probability of combined remission at 24-weeks in the two subgroups, as reported in the KM curve in Figure 3A (86% vs. 92% in UC; log-rank p <0.001), a significantly lower median combined remission time was observed in the UC subgroup (5.58 months, 95%CI 5.42 -6.39 months) compared to CD (median 7.23 months, 95%CI: 6.87-7.35 months).

In the KM analysis on persistence in therapy at 24-weeks, in 81 patients (87.1%) persistence at 24-weeks of follow-up, with a higher rate of therapy continuation among CD patients (90.7% vs. 84% in UC, p=0.373) after a significantly higher median time (7.15 months, 95%CI: 6.55-7.32 months vs. 5.65 in UC, 95%CI: 5.42-6.87 months, p<0.05) was observed (Fig. 3B).

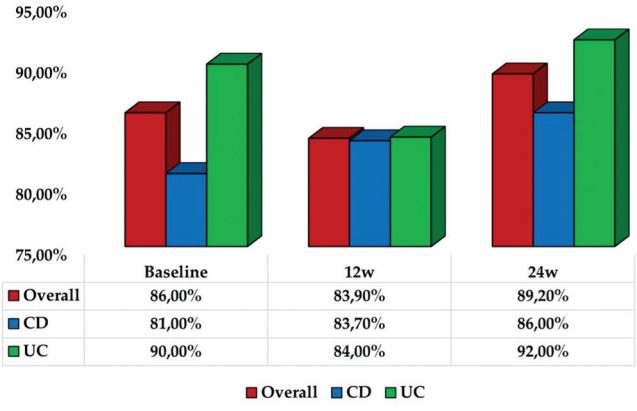

Fig. 2. Week-12 and Week-24 effectiveness, in terms of combined remission [Steroid-Free Clinical Remission (SFCR) plus Biochemical Remission (BR)], both overall (red) and in the Crohn's disease (CD, blue) and ulcerative colitis (UC, green) subgroups.

Table III. Univariable Cox regression model for 24-weeks combined remission probability

	Univariable Analysis		
	SFCR+BR (n=83)	No Remission (n=10)	HR (95% CI); p
Age, years	53.2 (16.4)	54.4 (11.9)	0.99 (0.98; 1.00); 0.153
Female sex	39 (47)	4 (40)	1.12 (0.72; 1.74); 0.616
Smoking habit	6 (7.2)	1 (10.0)	1.07 (0.47; 2.47); 0.870
Diagnosis			2.21 (1.39; 3.51); 0.001
CD	37 (44.6)	6 (60)	
UC	46 (55.4)	4 (40)	
Duration of disease, years	13.0 (7.0-18.5)	9.0 (5.5-19.2)	1.00 (0.98; 1.02); 0.995
Resection	24 (28.9)	1 (10)	0.66 (0.40; 1.08); 0.099
EIMs	13 (15.7)	1 (10)	1.25 (0.68; 2.27); 0.469
C-reactive protein	0.00 (0.00-0.00)	1.60 (0.00-5.70)	0.95 (0.87; 1.03); 0.210

SFCR: steroid-free clinical remission; BR: biochemical remission; CD: Crohn's disease; UC: ulcerative colitis; EIMs: extraintestinal manifestations. HR: hazard ratio; 95%CI: 95% confidence interval. Qualitative data are expressed as absolute and relative percentage frequency, whilst quantitative as median and interquartile range (IQR), as appropriate.

Safety and Discontinuation

In total, we reported 25 AEs in 23 patients, of which the most represented were 6 SARS-CoV-2 infections and 9 mild injection site reactions (Table IV). The rate of adverse events observed in the UC subgroup was higher, although not significantly (30% vs. 18.6% in CD, p=0.235).

Twelve patients (12.9%) discontinued SC-VDZ and restarted IV-VDZ. No patients needed to swap a different class of biologics. In depth, 10 patients (80% UC) discontinued treatment due to AEs, (six due to mild and severe site injection reaction and four due to disease flare), while only two preferred to return to IV administration.

DISCUSSION

In our study, enrolling a large cohort of patients with IBD who switched from IV-VDZ to SC-VDZ, combined SFCR plus BR was achieved in 89.2%, 92%, and 86% of patients with UC and CD, respectively. In addition, 83.9% of patients (83.7% CD and 84% UC) achieved SFCR plus BR after 12-weeks after switching to SC-VDZ. In line with our findings, Volkers et al. [7] reported in a cohort of 135 IBD patients a BR and clinical-steroid-free remission at week 24 in 60% and 47.6% of CD patients and 71% and 80% of UC patients, respectively, after switching from IV-VDZ to SC-VDZ. They explained the decrease in remission rates in CD patients by the relatively low number of CD patients that reached the 24-week follow-up period. Interestingly, our findings demonstrated that a diagnosis of UC is a predictor of a higher probability of combined remission compared to CD after switching to SC-VDZ at 24 weeks. Moreover, UC patients have a significantly lower median combined remission achievement time than CD patients, as previously reported with the IV formulation [27]. The discovery of significant differences in drug formulation

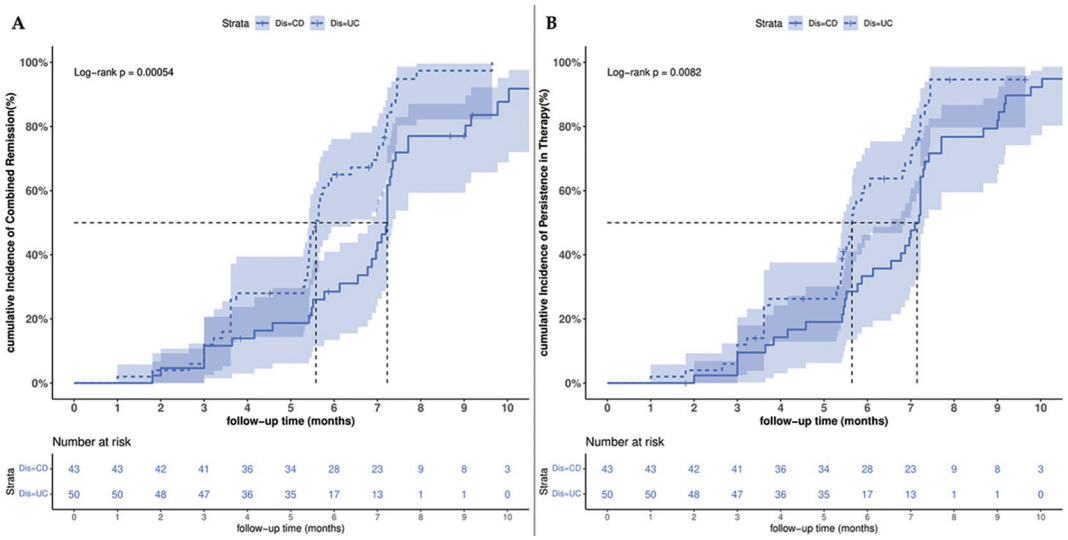

Fig. 3. Kaplan-Meier (KM) curves showing the cumulative incidence, at last follow-up, of combined remission, i.e. Steroid-Free Clinical Remission (SFCR) plus Biochemical Remission (BR) [PANEL A], and persistence in therapy (PANEL B), stratified for the type of disease, i.e. Crohn's disease (CD, blue solid line) and ulcerative colitis (UC, blue dashed line), respectively.

Table IV. Safety outcome in the study sample (93)

Adverse events	N=25 (out of 93 patients)
Mild AEs* (Grade 1 CTCAE)	
Injection site reaction	9 (36)
New onset arthralgia	2 (8)
SARS-CoV-2 infection	6 (24)
Uveitis	1 (4)
Moderate/Severe AEs* (Grade 2 CTCAE)	
Urticarial reaction	1 (4)
Dental abscess	1 (4)
Reactivation of disease	2 (8)
Severe AEs* (Grade 3 CTCAE)	
Injection site reaction	1 (4)
Reactivation of disease	2 (8)

AE: adverse events; CTCAE: Common Terminology Criteria for Adverse Events. Relative percentage frequencies are computed on the total of adverse events observed.

effectiveness at 24 weeks, depending on the diagnosis type, has the potential to provide improved guidance for physicians when considering a switch to subcutaneous administration. Furthermore, Bergqvist et al. [6] recently published a real-world study on a Swedish cohort of 89 patients, showing that clinical indices, remission rates, plasma CRP levels and quality-of-life scores remained unchanged, as did the frequency of AEs before and after switching, with drug persistence at 6 and 12 months of 95.5% and 88.5%, respectively.

Interestingly we observed an improvement in the BR rate in nine patients with SFCR at baseline at 24-weeks. This result could be explained by the pharmacokinetic optimization related to the SC switch, even if it is unclear whether average serum concentrations are related to biochemical responses [6]. In the VISIBLE I and VISIBLE II trials, the SC dose was selected to provide comparable drug exposures to 300 mg vedolizumab every-8 weeks; this formulation did not demonstrate any statistically significant difference as compared to IV administration, while safety and tolerability profiles were equally favorable [28, 29]. Nevertheless, it has been suggested that since the SC formulation maintains an increased plasma drug concentration compared to the IV formulation, SC-VDZ may represent a good strategy to improve drug efficacy, considering that some studies showed that higher VDZ trough levels during maintenance therapy were associated with improved clinical outcomes and histological healing [30-32]. Indeed, in our study, the five patients who were previously on IV-VDZ therapy every-4 weeks, still maintained remission.

Of note, the KM analysis of persistence in therapy showed a higher rate of therapy continuation among CD patients (90.7% vs. 84% in UC). This finding might be explained by the higher, though not significant, adverse event rate and discontinuation observed in the UC subgroup.

Regarding safety, we assessed 25 AEs, predominantly site reactions and infections, along with a few cases of new-onset extra-intestinal manifestation. All four patients who had a disease worsening, regained remission switching back to IV formulation; despite this, we cannot consider disease flare as an SC formulation-related side effect, due to the small number of events and the potential confounding factors.

Beyond effectiveness and safety, switching to SC formulation may provide considerable advantages for both patients and health systems. Recently, in a real-world study of a French cohort, Oppe et al. [33] showed that the introduction of SC-VDZ after IV induction is expected to produce substantial cost savings for a health plan. Indeed, the self-administration of the drug supported by appropriate training is not only time- and money-sparing for patients, due to reduction of travel to the healthcare institution, but is also associated with an increased quality of life.

In clinical practice, the decision-making process driving IBD patients and their physicians to choose the right treatment or switch the current therapy is a challenging experience, with the IBD physician willing to motivate patients to the most acceptable and suitable route of drug administration according to the disease characteristics and the clinical evidence and the patient to become aware and engaged in disease management [34].

This study has some limitations, including the relatively small sample size and short follow-up period, which may not provide sufficient robustness for the time-dependent analysis of 24-weeks effectiveness; the absence of objective effectiveness (e.g. fecal calprotectin levels or endoscopy data); the absence of a therapeutic drug monitoring, and the absence of data on changes in quality of life.

CONCLUSIONS

Switching from IV-VDZ to SC-VDZ can be considered a reasonably safe and effective treatment for maintaining remission in patients with IBD for up to 24-weeks of follow-up. Further studies with a larger sample size and a longer follow-up, as well as exploring patients' satisfaction and healthcare direct and indirect costs, are required.

IBD UNIT-CEMAD (Daniela Pugliese, Luisa Guidi, Loris Riccardo Lopetuso, Marco Pizzoferrato, Norma Alfieri, Fabiola De Biasio, Gabriele Rumi, Irene Mignini, Lucrezia Laterza, Laura Parisio, Carlo Romano Settanni, Valentina Giorgio, Fabrizio Pizzolante, Nicoletta De Mattheis, Maria Assunta Zocco, Maria Elena Ainora, Tiziana Bernabei, Daniele Napolitano, Elisa Schiavoni, Laura Turchini, Valeria Amatucci, Luciana Nicola Giordano, Valentina Benini, Carla Conticelli, Anna De Vito, Alessandra Di Massimo, Antonia Lorusso, Valentina Pettinari, Carmela Virone, Valentina Petito, Letizia Masi, Francesca Maria Calà Palmarino, Caterina Fanali, Vincenzina Mora, Alfredo Papa, Antonio Gasbarrini and Franco Scaldaferri).

Conflicts of interest: D.P. received speaker fees and/or advisory board fees from AbbVie, Janssen, MSD, Pfizer, Galapagos and Takeda. F.S. received speaker fees and/or advisory board fees from, Janssen, MSD, Pfizer and Takeda, Sandoz, Celltrion, Ferring. A.A. has received consulting/advisory board fees from AbbVie, Allergan, Amgen, Arena, Biogen, Bristol-Myers Squibb, Celgene, Celltrion, Eli-Lilly, Ferring, Galapagos, Gilead, Janssen, MSD, Mylan, Pfizer, Protagonist Therapeutics, Roche, Samsung Bioepis, Sandoz, Takeda; speaker's fees from AbbVie, Amgen, Arena, Biogen, Bristol-Myers Squibb, Eli-Lilly, Ferring, Galapagos, Gilead, Janssen, MSD, Novartis, Pfizer, Roche, Samsung Bioepis, Sandoz, Takeda, Tigenix; research support from

Biogen, MSD, Pfizer and Takeda. A.G. is an advisory board member for Actial Farmaceutica, Alfa Sigma, Zambon and Aboca. For the rest of authors: no conflict to declare.

Authors' contributions: L.P. and C.R.S. the concept and design of the study; L.P., C.R.S., S.V., L.L., L.R.L., D.N., E.S., L.T., C.F., N.A., and M.P. data acquisition; P.C.P. statistical analysis; L.P., C.R.S., S.V., D.P., and F.S. interpreted the results; L.P., C.R.S., S.V. drafted the manuscript, A.P., A.A., A.G., D.P. and F.S. revised the content. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

REFERENCES

1. Juillerat P, Grueber MM, Ruetsch R, Santi G, Vuillèmoz M, Michetti P. Positioning biologics in the treatment of IBD: A practical guide – Which mechanism of action for whom? Curr Res Pharmacol Drug Discov 2022;3:100104. doi:10.1016/j.crphar.2022.100104
2. Hazel K, O'Connor A. Emerging treatments for inflammatory bowel disease. Ther Adv Chronic Dis. 2020;11:2040622319899297. doi:10.1177/2040622319899297
3. 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. doi:10.1053/j.gastro.2019.08.027
4. Stoner KL, Harder H, Fallowfield LJ, Jenkins VA. Intravenous versus Subcutaneous Drug Administration. Which Do Patients Prefer? A Systematic Review. Patient 2014 Jul 12. doi:10.1007/s40271-014-0075-y
5. 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. doi:10.1093/ecco-jcc/jjab133
6. Bergqvist V, Holmgren J, Klintman D, Marsal J. Real-world data on switching from intravenous to subcutaneous vedolizumab treatment in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2022;55:1389-1401. doi:10.1111/apt.16927
7. 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. doi:10.1111/apt.17153
8. 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. doi:10.1093/ecco-jcc/jjac009
9. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;1:514. doi:10.1016/s0140-6736(80)92767-1
10. Naegeli AN, Hunter T, Dong Y, et al. Full, Partial, and Modified Permutations of the Mayo Score: Characterizing Clinical and Patient-Reported Outcomes in Ulcerative Colitis Patients. Crohns Colitis 360 2021;3:otab007. doi:10.1093/crocol/otab007
11. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625–1629. doi:10.1056/NEJM198712243172603
12. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med 2005;353:2462-2476. doi:10.1056/NEJMoa050516
13. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006;55:749–753. doi:10.1136/gut.2005.082909
14. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies. Actas Dermosifiliogr 2021;112:90–92. doi:10.1016/j.ad.2019.05.009
15. Moritz S. A General Multivariate Imputation Framework. 2022 [cited 2023 Mar 21]; Available from: https://github.com/SteffenMoritz/imputeR/issues
16. Wickham MH. Package "ggpt2" Type Package. GitHub - tidyverse/ggplot2: An implementation of the Grammar of Graphics. 2014. Available from: https://github.com/tidyverse/ggplot2
17. Patil I. Visualizations with statistical details: The "ggstatsplot" approach. J Open Source Softw 2021;6:3167. doi:10.21105/joss.03167
18. Kassambara A. "ggplot2" Based Publication Ready Plots [R package ggpubr version 0.6.0]. 2023; Available from: https://CRAN.R-project.org/package=ggpubr
19. Dawson C. A "ggplot2" Extension Inspired by "GraphPad Prism". Available from: https://cran.r-project.org/package=ggprism
20. Ahlmann-Eltze C, Patil I. ggsignif: R Package for Displaying Significance Brackets for "ggplot2". Available from: https://psyarxiv.com/7awm6/
21. Kassambara A, Kosinski M, Biecek P. Package "survminer": Drawing Curves using "ggplot2." 2022; Available from: https://cran.r-project.org/web//packages//survminer/survminer.pdf
22. Therneau TM, Grambsch PM. A Package for Survival Analysis in S, version 2.38. Modeling Survival Data: Extending the Cox Model 2000; Available from: http://cran.r-project.org/package=survival
23. Therneau TM. Survival Analysis [R package survival version 3.5-5]. 2023; Available from: https://CRAN.R-project.org/package=survival
24. Stablein DM, Carter WH, Novak JW. Analysis of survival data with nonproportional hazard functions. Control Clin Trials 1981;2:149-159. doi:10.1016/0197-2456(81)90005-2
25. Schemper M, Wakounig S, Heinze G. The estimation of average hazard ratios by weighted Cox regression. Stat Med 2009;28:2473–2489. doi:10.1002/sim.3623
26. R: The R Project for Statistical Computing 2023. Available from: https://www.r-project.org/
27. Vasudevan A, Gibson PR, Van Langenberg DR. Time to clinical response and remission for therapeutics in inflammatory bowel diseases: What should the clinician expect, what should patients be told? World J Gastroenterol 2017;23:6385–6402. doi:10.3748/wjg.v23.i35.6385
28. 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. doi: 10.1053/j.gastro.2019.08.027
29. 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. doi:10.1093/ecco-jcc/jjab133
30. Volkers A, Straatmijer T, Duijvestein M, et al. DOP63 Real World Effectiveness, Safety and Pharmacokinetics of Switching Intravenous Vedolizumab Maintenance treatment to Subcutaneous Vedolizumab Therapy for Inflammatory Bowel Disease. J Crohns Colitis 2022;16(Supplement_1):i108–i109. doi:10.1093/ecco-jcc/jjab232.102
31. Pouillon L, Rousseau H, Busby-Venner H, et al. Vedolizumab Trough Levels and Histological Healing During Maintenance Therapy in Ulcerative Colitis. J Crohns Colitis 2019;13:970–975. doi:10.1093/ecco-jcc/jjz029

32. Ward MG, Sparrow MP, Roblin X. Therapeutic drug monitoring of vedolizumab in inflammatory bowel disease: current data and future directions. Therap Adv Gastroenterol 2018;11:1756284818772786. doi:10.1177/1756284818772786
33. Oppe M, Muresan B, Chan K, et al. Budget impact of introducing subcutaneous vedolizumab as a maintenance therapy in biologic-naïve and biologic-experienced patients with ulcerative colitis in France. Expert Rev Pharmacoecon Outcomes Res 2023;23:205-213. doi:10.1080/14737167.2023.2160322
34. Denesh D, Carbonell J, Kane JS, Gracie D, Selinger CP. Patients with inflammatory bowel disease (IBD) prefer oral tablets over other modes of medicine administration. Expert Rev Gastroenterol Hepatol 2021;15:1091–1096. doi:10.1080/17474124.2021.1898944