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Alimentary Tract

Switching from VEDOlizumab intravenous to subcutaneous formulation in ulcerative colitis patients in clinical remission: The SVEDO Study, an IG-IBD study

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ABSTRACT

Background: The administration of biological drugs in inflammatory bowel diseases (IBD) is increasingly moving from intravenous to subcutaneous formulations.
Aims: To evaluate the efficacy and safety of vedolizumab subcutaneous administration after switching from intravenous administration in ulcerative colitis (UC) patients in corticosteroid-free clinical remission.

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Methods: An observational, multicentre, prospective study was conducted by the Italian Group for the study of IBD (IG-IBD). UC patients in clinical remission (pMAYO < 2) not receiving steroids for > 8 months before the switch, and with at least 6 months of follow-up were included. Switch from intravenous to subcutaneous vedolizumab was defined as successful in patients not experiencing a disease flare (pMAYO ≥ 2) or needing oral steroids or stopping subcutaneous vedolizumab during the 6 months of follow-up after the switch.

Results: Overall, 168 patients were included. The switch was a success in 134 patients (79.8%). Vedolizumab retention rate was 88.7% at month six. C-reactive protein and faecal calprotectin values did not change after the switch ($p = 0.07$ and $p = 0.28$, respectively). Ten of the 19 patients who stopped subcutaneous formulation switched back to intravenous formulation recapturing clinical remission in 80%. Side effects were observed in 22 patients (13.1%).

Conclusion: Effectiveness of switching from intravenous to subcutaneous vedolizumab formulation in UC patients in steroid-free clinical remission is confirmed in a real-world setting.

1. Introduction

The chronic inflammatory disease ulcerative colitis (UC), which affects the rectum and possibly the colon, can cause structural bowel damage, decrease in quality of life, and disability [1]. Mesalamine, corticosteroids, and eventually immunomodulators are used to treat UC as conventional therapies. Targeted therapies, including anti-tumour necrosis factor (TNF)-α, vedolizumab, ustekinumab, anti-JAK inhibitors (tofacitinib, filgotinib), and ozanimod are indicated for patients failing conventional therapy [2].

Despite the fact that new molecules are becoming available for UC treatment, a simpler route of administration, from intravenous to oral or subcutaneous, has been associated to a lower impact on the healthcare system and increased quality of life for UC patients [3]. Vedolizumab is a first in class biological drug: it is a humanised monoclonal gut-specific antibody targeting a4ß7 integrins and preventing lymphocytes trafficking into the gut mucosa. Vedolizumab has shown to be effective for inducing and maintaining clinical remission in UC with a good safety profile [4]. This drug has been classically administered intravenously, with an impact on hospital organization, especially when many patients are treated in a centre or during COVID-19 pandemic [5,6].

Recently, the randomized clinical trial VISIBLE 1 has been published [7]. In this study, UC patients, after an induction of intravenous vedolizumab 300 mg at weeks 0 and 2, in case of clinical response, were randomized at week 6 to intravenous vedolizumab 300 mg every 8 weeks, subcutaneous vedolizumab 108 mg every 2 weeks, or placebo. Subcutaneous formulation effectiveness and safety were comparable to that of intravenous formulation. Switching from long-term intravenous vedolizumab was not analysed in this study.

Subcutaneous administration of vedolizumab has several potential advantages over intravenous administration, including a lighter burden on medical resources and greater patient convenience. Increased challenges in ensuring therapy compliance, a potential preference for intravenous treatment, and local skin reactions to subcutaneous injections are potential drawbacks of subcutaneous therapy [8].

There are currently few studies in the literature that have analysed the effectiveness and safety of the subcutaneous formulation of vedolizumab in patients with UC treated for a long time with intravenous vedolizumab [9–12]. Thus, the aim of this study was to assess the efficacy and safety of subcutaneous formulation of vedolizumab after switching from intravenous formulation in patients affected by UC in clinical remission in a large, real-life cohort of Italian patients.

2. Materials and methods

The SVEDO study was an observational, multicentre, prospective study on adult patients affected by UC that switched from intravenous to subcutaneous formulation of vedolizumab conducted by the Italian Group for the study of IBD (IG-IBD) in 19 reference centres throughout Italy.

The recruitment of the patients started on 1st June 2021, and finished on 15th September 2022. Follow-up ended on 15th March 2023.

Inclusion criteria were:

- UC in clinical remission (defined as a partial MAYO score < 2) [13] not receiving oral systemic or low absorbable steroids since at least 8 months before the switch with intravenous vedolizumab.
- At least 6 months of follow-up after the switch.
- Willingness of the patient to share their clinical data.

Physicians at participating centres selected patients to be switched to the subcutaneous formulation based on their clinical judgement and did not offer it to all patients consecutively.

We chose to include only patients with UC because the registration study of subcutaneous vedolizumab in Crohn's disease (CD) had not yet been published at the time of writing the protocol [14].

Exclusion criteria were:

- Total colectomy
- No clinical data 6 months before the switch, at the switch, 6 months after the switch.

All patients were prospectively followed at the outpatient clinics by expert clinicians on inflammatory bowel disease with regular appointments. Clinical, biochemical, and endoscopic evaluation were performed during follow-up at physician's discretion and at months six all patients were re-evaluated. The following data were collected:

- At T0: date at switch, age at T0, smoking habit, sex, disease extension at worst diseases stage (E1, E2, E3), previous anti-TNF treatment, months of intravenous vedolizumab, disease duration, vedolizumab frequency of administration
- At T0 and T6: C-reactive protein (CRP), calprotectin, pMAYO, thiopurines use, side effects (in the six months before and after the switch from intravenous to subcutaneous formulation)
- At T6: oral steroids, vedolizumab retention, reason for vedolizumab discontinuation, UC-related hospitalization, UC-related intestinal surgery, switch back to intravenous formulation.

Measures of safety were planned to include clinical and laboratory adverse events, included administration reactions.

The switch from intravenous to subcutaneous vedolizumab was defined as successful in patients not experiencing a disease flare (pMAYO $\geq$ 2) or needing oral steroids or stopping subcutaneous vedolizumab during the 6 months of follow-up after the switch. The following variables were evaluated for failure of the switch: age at T0, smoking habit at T0, sex, disease extension, previous anti-TNF treatment, duration of intravenous vedolizumab therapy, CRP at T0, calprotectin at T0, pMAYO (0 / 1) at T0, thiopurine therapy at T0.

In addition, other endpoints included rate of subcutaneous vedolizumab discontinuation, overall remission status, changes in C-reactive protein (CRP) as well as changes in faecal calprotectin levels.

2.1. Statistical analysis

Descriptive statistics was used to characterize the patient population. Results are provided as mean and standard deviation or median and interquartile range (according to normal distribution at D'Agostino-Pearson test) for continuous variables and as frequencies and percentages for categorical variables. The influence of risk factors on the outcome was analysed with logistic regression analysis (backward stepwise selection; cut-off for continuous variable was chosen according to Youden index).

The pMAYO, CRP, calprotectin value at T0 were compared with their values at T6 with Paired sample *t*- test according to distribution of the values.

A p-value of $<$ 0.05 was considered to be statistically significant. Statistical analyses were performed using the IBM SPSS Statistics v25 (IBM Corporation).

2.2. Ethical considerations

The study protocol was approved by the IG-IBD scientific committee, and subsequently, by the Ethical Committee of the coordinating centre (Turin, Protocol N° 0038452; April 8th, 2021), and of each participating centre. All patients received written information and signed the consent for clinical data collection as well as the privacy statement form. Shared database was used for anonymous data collection. The study followed the principles of the Declaration of Helsinki.

3. Results

We recruited 168 patients affected by UC. The baseline characteristics of the recruited patients are reported in Table 1.

3.1. Clinical recurrence and therapy discontinuation

Thirty-four (20.2%) patients experienced clinical recurrence or required either oral steroids or vedolizumab withdrawal during the first 6 months of follow-up after the switch (Fig. 1).

In particular, 24 patients (14.3%) experienced a relapse in disease activity, 4 patients (2.4%) needed oral steroids, 19 patients (11.3%) stopped vedolizumab during the 6 months of follow-up after the switch. The reasons for stopping vedolizumab were drug failure in 7 patients, adverse event in 9 patients, patient's choice in 1 patient (other in 2 patients). Of these, 10 patients (52.6%) switched back to intravenous formulation and, out of them 80% recaptured clinical remission. amongst the patients who did not stop vedolizumab despite loss of remission and did not require treatment with oral steroids, 7 patients had pMAYO = 2 and 6 patients had pMAYO = 3 (mild disease activity) and 2 patients had pMAYO = 5 (moderate disease activity). One patient was hospitalized during the 6-months follow-up. One patient underwent colectomy during the 6-months follow-up. At T6 no patients were on thiopurine therapy.

Table 1
Baseline characteristics of the included patients (n = 168).

Characteristics	
Age (years), mean ± SD	52.7 ± 15.6
Disease duration (years), mean ± SD	14.0 ± 8.7
Gender (M), *n* (%)	99 (58.9)
Smoking habit, *n* (%); [162]	
never	112 (69.1)
current	7 (4.3)
previous	43 (26.6)
Montreal classification, *n* (%)	
E1	13 (7.7)
E2	68 (40.5)
E3	87 (51.8)
Previous anti-TNF (Y), *n* (%)	87 (51.8)
Duration of therapy with i.v. vedolizumab, mean ± SD	27.2 ± 15.7
Clinical activity, pMAYO (0/1)	141/27
Faecal calprotectin (mg/kg), mean ± SD, [127]	84.0 ± 90.7
CRP (mg/L), mean ± SD; [127]	1.7 ± 2.6
Thiopurines (Y), *n* (%)	3 (1.8)
Frequency of administration of VDZ 300 mg =8 w, *n* (%)	142 (84.5)

Numbers in brackets indicate patients with available data
n = number of patients; SD = standard deviation; M = male; F = female; Y = yes; E1 = rectum; E2 = up to splenic flexure; E3 = extensive colitis; TNF = tumour necrosis factor; i.v. = intravenous; CRP = C-reactive protein; VDZ = vedolizumab; w = weeks

The risk factors for switch failure are reported in Table 2.

At multivariate analysis, none reached statistical significance (see Table 3).

3.2. Biochemical tests

Mean CRP values at T6 did not differ from T0 values (1.5 ± 2.0 mg/L at T6 versus 1.8 ± 2.7 mg/L at T0 [in patients with both T0 and T6 values], p = 0.07). Mean faecal calprotectin levels at T6 did not differ from T0 values (102.2 ± 169.8 mg/kg at T6 versus 85.1 ± 92.2 mg/kg at T0 [in patients with both T0 and T6 values], p = 0.28).

3.3. Side effects

During the first 6 months of the subcutaneous formulation, 22 patients (13.1%) experienced in total 26 different side effects, including 4 rheumatologic side effects, 4 injection site reactions, 3 incidental cancers (1 prostate cancer with bone metastases and 2 cases of early stage breast cancer), 3 allergic side effects, 1 UC complication, and 11 other not specified side effects.

4. Discussion

In our study, 134 of 168 patients (79.8%) had a success in switching from intravenous to subcutaneous vedolizumab formulation. In particular, at month six, the retention rate for vedolizumab was 88.7%. At multivariate analysis, no predictor of switch success was found. After the switch, the levels of CRP and calprotectin did not differ significantly from T0 values (p = 0.07 and p = 0.28, respectively). The subcutaneous formulation was associated with side effects in 22 out of 168 patients (13.1%), including 4 cases of rheumatological side effects, 4 cases of dermatological side effects, 3 cases of allergic reactions, and 3 cases of malignancy. Our data confirm the preliminary evidence of a safe and effective switch from intravenous to subcutaneous vedolizumab [9–12].

The present study is the largest, multi-centre study on UC patients in durable clinical remission with intravenous vedolizumab formulation that were switched to subcutaneous formulation with a fixed follow-up timepoint for all included patients (6 months). Our study points out that switch from intravenous to subcutaneous

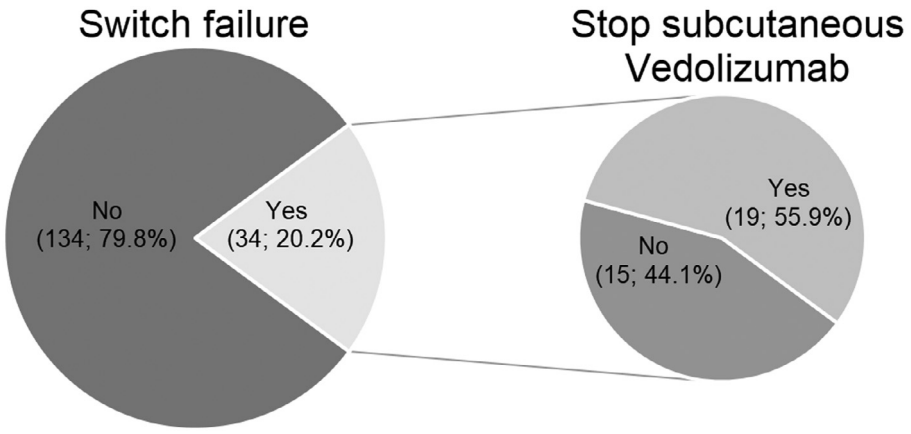

Fig. 1. Pie-in-the-pie chart depicting switch failure rate (on the left) and the rate of subcutaneous vedolizumab withdrawal at month 6 in patients that experienced switch failure (on the right). Switch failure was defined for at least one of the following: loss of remission (pMAYO ≥ 2), administration of oral steroids, or stop subcutaneous vedolizumab.

Table 2
Predictors of switch failure.

Predictors	Switch failure no n = 134	Switch failure yes n = 34	p value
Age at T0, years (mean, SD)	53.0 (15.9)	51.4 (14.2)	0.59
Never smokers/current smokers/ex-smoker/N.A.	91/6/33	21/1/10	0.77
Sex (F/M)	52/82	17/17	0.25
E2/E3	54/71	14/16	0.84
Previous anti-TNF, n/tot (%)	68/134 (50.7)	19/34 (55.9)	0.70
Duration of intravenous therapy, months (mean, SD)	27.6 (16.0)	25.5 (14.6)	0.49
CRP at T0, mg/L (mean, SD)	1.6 (2.6)	1.8 (2.7)	0.80
Faecal calprotectin, mg/kg (mean, SD)	74.2 (84.1)	120.1 (105.7)	0.02
pMAYO (0/1)	116/18	25/9	0.07
Thiopurine therapy at T0 (Y/N)	2/132	1/33	0.50
Frequency of administration of VDZ (8 w/4–6 w)	116/18	26/8	0.15

n = number; SD, standard deviation; N.A. = not available; F, female; M, male; E2, left side colitis; E3, extensive colitis; TNF = tumour necrosis factor; tot = total; CRP = C-reactive protein; Y = yes; N = no; VDZ = vedolizumab; w = weeks

Table 3
Predictors of switch complete success at multivariate analysis.

Predictors	O.R.	95% CI	p value
Sex = F	0.62	0.24 – 1.64	0.34
Smoking habit = never	1.03	0.38 – 2.83	0.95
Age < 50 years	0.97	0.36 – 2.61	0.95
Disease extension = E1 or E2	0.62	0.24 – 1.58	0.32
Previous anti-TNF = no	1.10	0.42 – 2.91	0.85
Months of vedolizumab < 23 months	1.48	0.54 – 4.06	0.44
CRP < 0.22 mg/L	5.04	0.63 – 40.53	0.13
Faecal calprotectin < 75 mg/kg	2.38	0.95 – 5.94	0.06
pMAYO = 0	2.75	0.98 – 7.68	0.05
Frequency of administration of VDZ 300 mg = 8 w	1.13	0.33 – 3.93	0.85

F = female; O.R. = Odds ratio; E1 = rectum; E2 = left side colitis; VDZ = vedolizumab; w = weeks

formulation is a feasible strategy, despite a not negligible rate of disease relapse. This result was confirmed by objective biomarkers like CRP and faecal calprotectin. These data, in addition with the obvious advantages for the patients in terms of working days missed and travel expenses and the healthcare system, could contribute to the reduction of the intravenous route of administration of biological drugs in the maintenance phase in the majority of IBD patients. Regarding the factors influencing switch success, despite none reached statistical significance at multivariate analysis, a trend in predicting switch success was found for calprotectin < 75 mg/kg (p = 0.06) and pMAYO 0 (versus 1, p = 0.05), although it is impossible to know if patients had been kept on the intravenous formulation, disease recurrence or corticosteroid use or drug discontinuation would not have occurred.

In the VISIBLE I study, the discontinuation rate of the subcutaneous formulation of vedolizumab was approximately 30% after 52 weeks [7], but this figure is not comparable with ours because patients were not in stable clinical remission at the time of switch. The VISIBLE I trial reported a corticosteroid-free clinical remission of about 50% at week 52 but, for the same reason of that of drug retention, this figure is not comparable with that of our study.

Pharmacokinetic characteristics for subcutaneous and intravenous preparations differ generally. Lower peak concentrations, limited bioavailability, and slow absorption are the results of subcutaneous administration [15]. When compared to the intravenous vedolizumab treatment group, the subcutaneous vedolizumab treatment group in the VISIBLE 1 trial had higher vedolizumab serum trough concentrations [7]. High vedolizumab serum trough

concentrations and stable systemic drug exposure during subcutaneous vedolizumab treatment may improve efficacy outcomes, according to prior research that linked these factors to favourable therapeutic outcomes during intravenous maintenance treatment [16]. Although vedolizumab serum level data were not available in our observational study as they were not routinely performed in most centres, our real-world clinical data confirm the feasibility of this switch.

In our study, only 10 patients (6.1%) switched back to intravenous formulation, with an 80% of success in recapturing clinical remission. This figure is comparable with that of previous published studies [9,12] and confirms that, even in the few patients in which switch to subcutaneous formulation was not a success, switching back to intravenous formulation is a feasible strategy.

Some limitations of our study deserve to be discussed. First, the comparator for our patients are the same patients before the switch to intravenous to subcutaneous formulation. To reduce bias, we excluded patients with clinical disease activity. Second, since the SVEDO study was a non-interventional study, each clinician in each centre proposed the switch to subcutaneous administration based on their choice and regional availability: as patients had to be willing to switch to subcutaneous formulation, there is a potential risk for bias as more therapy refractory patients might be less willing to switch to the subcutaneous formulation, even if in current remission. Third, we did not assess endoscopic outcomes due to the fact that only few patients underwent colonoscopy in the six-month follow-up. Finally, we did not evaluate vedolizumab trough levels because these values are not generally available in clinical practice [17].

Conversely, the current study has a longer follow-up time than the British cohort and included more UC patients compared to previous studies [9–12]. In particular, the strength of this study lies in the systematic prospective follow-up with pre-defined clinically relevant endpoints, the substantial cohort size, and the multicentre nature. Due to the participation of both academic and non-academic hospitals and the patient characteristics of our cohort (more than 50% anti-TNF experienced), our data reflects a daily practice that justifies generalizability. In addition, our this is the first real-word study that formally defined an outcome of switch success (less than 15% of patients with disease activity or need oral steroids or stop vedolizumab during the 6 months of follow-up after the switch).

In conclusion, the switch from intravenous to subcutaneous vedolizumab formulation is a safe and effective choice in UC patients in durable clinical remission, despite a not negligible rate of disease relapse is possible.

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