Real-world experience of switching from intravenous to subcutaneous vedolizumab maintenance treatment for inflammatory bowel diseases

Volkers, A.; Straatmijer, T.; Duijvestein, M.; Sales, A.; Levran, A.; Schaik, F. van; ... ; Dutch Initiative Crohn Colitis

Galápagos

JAK to the future:

a patient-centric choice in UC

Satellite symposium at UEG Week 2022

Professor
Alisa Hart

Professor
Raja Atreya

Professor
Alessandro Armuzzi

In person and online
Monday 10 October 2022
12:30–13:30 CEST

Find out more

For HCPs only | This symposium is not affiliated with UEG
August 2022 | GL-IBD-NA-202205-00001

Received: 26 April 2022 | First decision: 16 May 2022 | Accepted: 7 July 2022

DOI: 10.1111/apt.17153

AP&T Alimentary Pharmacology & Therapeutics WILEY

Real-world experience of switching from intravenous to subcutaneous vedolizumab maintenance treatment for inflammatory bowel diseases

Adriaan Volkers[1] | Tessa Straatmijer[1,2] | Marjolijn Duijvestein[3] | Amber Sales[1] | Amit Levran[1] | Fiona van Schaik[4] | Jeroen Maljaars[2] | Krisztina Gecse[1] | Cyriel Ponsioen[1] | Joep Grootjans[1] | Jurij Hanzel[5] | Greetje Tack[6] | Jeroen Jansen[7] | Frank Hoentjen[3,8] | Nanne de Boer[9] | Sander van der Marel[10] | Gerard Dijkstra[11] | Bas Oldenburg[4] | Mark Löwenberg[1] | Andrea van der Meulen[2] | Geert D'Haens[1] | on behalf of the IBD center Amsterdam and the Dutch Initiative on Crohn and Colitis

[1]Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) Research Institute, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[2]Department of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

[3]Department of Gastroenterology, Radboud University Medical Center, Nijmegen, The Netherlands

[4]University Medical Centre Utrecht, Utrecht, The Netherlands

[5]Department of Gastroenterology, UMC Ljubljana, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[6]Medical centre Leeuwarden, Leeuwarden, The Netherlands

[7]OLVG, Amsterdam, The Netherlands

[8]Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, Canada

[9]Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology Endocrinology Metabolism Research Institute, Amsterdam University Medical Centre, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[10]Haaglanden Medical Centre, The Hague, The Netherlands

[11]University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

Correspondence
Adriaan Volkers, Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) Research Institute, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.
Email: a.g.volkers@amsterdamumc.nl

Summary

Background: Subcutaneous (SC) vedolizumab is effective in inflammatory bowel diseases (IBD) when administered after induction with two infusions.

Aim: To assess the effectiveness, safety and pharmacokinetics of a switch from intravenous (IV) to SC maintenance vedolizumab in patients with IBD

Methods: In this prospective cohort study, patients with IBD who had ≥4 months IV vedolizumab were switched to SC vedolizumab. We studied the time to discontinuation of SC vedolizumab, adverse events (AEs), changes in clinical and biochemical outcomes and vedolizumab concentrations at baseline, and weeks 12 and 24.

Adriaan Volkers and Tessa Straatmijer are shared first authors.Andrea van der Meulen and Geert D'Haens are shared last authors.

The Handling Editor for this article was Professor Dr. Sreedhar Subramanian, and it was accepted for publication after full peer-review.

Results: We included 82 patients with Crohn's disease (CD) and 53 with ulcerative colitis (UC). Eleven (13.4%) patients with CD and five (9.4%) with UC discontinued SC vedolizumab after a median of 18 (IQR 8–22) and 6 weeks (IQR 5–10), respectively. Four patients with CD switched to a different drug due to loss of response, nine switched back to IV vedolizumab due to adverse events, and three due to needle fear. Common AEs were injection site reactions ($n = 15$) and headache ($n = 6$). Median clinical and biochemical disease activity remained stable after the switch. Median serum vedolizumab concentrations increased from 19 μg/ml at the time of the switch to 31 μg/ml 12 weeks after the switch ($p < 0.005$).

Conclusions: Switching from IV to SC vedolizumab maintenance treatment is effective in patients with CD or UC. However, 9% of patients were switched back to IV vedolizumab due to adverse events or fear of needles.

1 | INTRODUCTION

Vedolizumab (VDZ) is a gut-selective, humanised monoclonal antibody directed towards α4β7 integrins, preventing their trafficking into the inflamed gut and possibly modulating the innate immunity.[1,2] Since 2014, VDZ has been registered for the treatment of patients with moderate to severe inflammatory bowel disease (IBD).[3,4] VDZ is typically administered intravenously (IV). Recently, two phase 3 trials (VISIBLE 1 and 2) demonstrated that a subcutaneous (SC) formulation of VDZ is effective and safe for patients with ulcerative colitis (UC) and Crohn's Disease (CD) directly after induction treatment with two infusions of VDZ.[5,6] These trials showed that in IBD patients who responded at week 6, 108 mg maintenance SC VDZ was superior to placebo for the primary endpoint of clinical and biochemical remission. Based on these trials, SC VDZ (Entyvio©) was approved by the European Medicines Agency as maintenance treatment in adult patients with moderate-to-severe active UC or CD in 2020. However, the VISIBLE 1 and 2 trials did not study IBD patients who have been treated with maintenance IV VDZ for a longer time. Therefore, we aim to prospectively follow IBD patients who are treated with maintenance IV VDZ for a longer period in a real-world setting.

SC and IV formulations in general have different pharmacokinetic profiles. SC administration leads to gradual absorption, incomplete bioavailability and lower peak concentrations.[7,8] VDZ infusion results in immediate systemic drug exposure and a high initial peak concentration. In the VISIBLE 1 trial, UC patients in the SC VDZ treatment group had higher VDZ serum trough concentrations when compared to the IV VDZ treatment group.[5] However, the overall average drug exposure was similar upon 108 mg SC VDZ every 2 weeks versus 300 mg IV VDZ every 8 weeks. As previous studies found an association between favourable therapeutic outcomes and high VDZ serum concentrations during IV maintenance treatment,[9–12] these high VDZ serum trough concentrations and stable systemic drug exposure using SC VDZ treatment may improve efficacy outcomes.

The option of a SC formulation of VDZ offers patients a choice regarding the route of administration. Previous studies evaluating patient preferences patient preference between SC and IV treatment is variable.[13,14] However, SC treatment might reduce direct health care costs (no infusion unit necessary), societal costs (no need to take time off work and for most patients to travel to infusion location) and environmental costs (no traffic to the hospital).[15,16]

In this study, we assessed drug discontinuation, effectiveness, safety and pharmacokinetics in a prospective real-world cohort of CD and UC patients, who switched from IV VDZ maintenance treatment to SC VDZ.

2 | METHODS

2.1 | Study design and participants

Data from two separate prospective, observational cohort studies in the Netherlands were combined. The first cohort was an open-label, real-life, single-centre, prospective cohort from the Amsterdam UMC, a tertiary IBD referral centre in The Netherlands. The second cohort consisted of IBD patients from nine other medical centres who registered their patients in the ICC (Initiative on Crohn and Colitis) registry: a prospective, nationwide observational registry of IBD patients starting novel IBD therapies in regular care in the Netherlands. Data collection was done using an electronic case report form (eCRF) with automated reminders to improve adherence to the protocol. During the period from July 2020 until August 2021, patients on maintenance IV VDZ switched to SC VDZ. Informed consent was obtained prior to enrolment. Follow-up lasted until November 2021. Therefore, the duration of follow-up differs amongst participants.

Inclusion criteria in both cohorts were: >4 months of IV VDZ treatment, an established diagnosis of IBD and ≥18 years of age. Patients with clinical or biochemical disease activity, concomitant corticosteroid use and an intensified IV VDZ dosing interval were allowed to enter the study. The only exclusion criterion for study enrolment was the need to discontinue IV VDZ in the next 4 months.

Prospective follow-up took place during scheduled outpatient clinic visits at weeks 12 and 24, designed to closely follow regular care. Not all patients underwent a study visit at each time point as this was a real-world study. Patients switching from an IV to SC formulation all received 108 mg SC VDZ once every 2 weeks. The datasets were merged since both patient cohorts had the same inclusion criteria, research aim, and a prospective follow-up with visits at weeks 12 and 24. There was a window of 4 weeks before or after the study visits. If during this time window a Harvey Bradshaw index (HBI) or simple clinical colitis activity index (SCCAI) was scored or if laboratory tests were performed, these data were collected in the eCRF. Data of SC VDZ discontinuation, adverse events and biochemical parameters, including VDZ serum concentrations, were documented at baseline and throughout the follow-up. As patients switched on different dates and the follow-up ended in November 2021, there was a difference in the duration of follow-up amongst patients.

2.2 | Outcomes and definitions

The main outcome was the proportion of patients discontinuing SC VDZ. Reasons for treatment discontinuation were documented by the treating physician. Patients who discontinued SC VDZ treatment due to a primary or secondary non-response, adverse events or fear of needles were considered treatment failures and classified as non-responders non-responder imputation (NRI). Patients who discontinued SC VDZ when moving abroad were censored. The discontinuation date was defined as the date of the last SC VDZ injection. In case the date of the last SC VDZ injection was not available, the discontinuation date reported in the electronic medical record was used. Additional outcomes included clinical remission, corticosteroid-free clinical remission (CSFR), biochemical remission and VDZ serum concentrations. Clinical remission was defined as SCCAI ≤ 2 in UC patients and HBI ≤ 4 in CD patients. Biochemical remission was defined as C-reactive protein (CRP) ≤ 5 mg/L and/or faecal calprotectin (FCP) ≤250 μg/g. All VDZ serum concentrations were measured at Sanquin (Sanquin diagnostics) and were measured using an assay, developed by Sanquin.[17] VDZ serum concentrations during SC treatment were measured at a random time after the last injection. VDZ serum concentrations were considered trough concentrations if they were measured between 12 and 21 days after the last SC VDZ injection.

Adverse events (AEs) were classified as probably not, possibly-, and probably-related to SC VDZ at the physician's discretion. Possibly- and probably-related AEs are described in this manuscript. Infections were classified as mild (no antibiotics or antiviral medication necessary), moderate (oral antibiotics or antiviral medication required) or severe (hospitalisation and/or IV antibiotics or anti-viral medication required). We assessed whether there was an association between infections, possibly- or probably-related AEs and VDZ serum concentrations. For this, we used the last measured VDZ serum concentration since this reflects the steady state concentration most accurately.

2.3 | Statistical methods

A power analysis was not performed as (1) we aimed to switch all eligible patients to SC VDZ, and (2) there was no control group, making a sample size calculation unfeasible. All analyses were performed on an intention-to-treat basis. Cumulative drug survival was visualised using a Kaplan–Meier curve. Continuous variables were presented as medians with interquartile ranges (IQR). Continuous variables were compared using the pairwise non-parametric Wilcoxon rank test. Variables associated with discontinuation were explored using logistic regression. Quartile analysis was used to determine if higher VDZ serum concentrations quartiles were associated with higher clinical, corticosteroid-free clinical, biochemical remission rates, and occurrence of adverse events. Logistic regression was performed as an additional test to examine an association between VDZ serum concentration and adverse events. Values of $p < 0.05$ were considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp.,).

2.4 | Ethical consideration

The medical ethics committee of the Amsterdam Medical Center reviewed this study and decided the study did not require approval since it was beyond the scope of the laws of medical research with humans. The ICC Registry cohort was reviewed and approved by the Committee on Research Involving Human Subjects at the Radboudumc (institutional review board: 4076).

3 | RESULTS

3.1 | Baseline characteristics

In total, 82 CD and 53 UC patients were included. Baseline characteristics are given in Table 1. Eighty-one patients (60.0%) were enrolled in the Amsterdam UMC cohort and 54 patients (40%) in the ICC cohort. Baseline characteristics per cohort are shown in Table S1. A vast majority of 124 patients (91.9%) were treated in a tertiary care centre. The median follow-up was 27 weeks (IQR 19–37), with a minimum of 5 weeks in a patient who discontinued due to adverse events and a maximum follow-up of 56 weeks. For those patients in which clinical and biochemical disease was assessed at the initiation of SC VDZ therapy, 92/130 (70.9%) and 94/131 (71.8%) of the patients were in corticosteroid-free clinical remission (CSFR) and biochemical remission, respectively. Forty-seven patients (34.8%) of the patients initiating SC VDZ, had a prior bowel resection.

3.2 | Drug survival

A total of 16 patients (11.9%) discontinued SC VDZ. These were 11 CD (13.4%) and 5 UC patients (9.4%), after a median of 18 (IQR

TABLE 1 Baseline characteristics at the time of the switch to SC VDZ

		CD ($n = 82$)	UC ($n = 53$)	Total ($n = 135$)
Age (years)	Median (IQR)	48 (30–63)	42 (31–61)	46 (30–62)
Female sex	*N* (%)	49 (59.8%)	24 (45.3%)	73 (54.1%)
Disease duration (years)	Median (IQR)	12 (6.8–27.3)	12 (6.5–19.5)	12 (7–26)
Follow-up (weeks)	Median (IQR)	27 (20–36)	27 (16–39)	27 (19–37)
Active smoking	*N* (%)	13 (15.9%)	3 (5.7%)	16 (12.2%)
IV vedolizumab treatment duration (months)	Median (IQR)	19 (11–41)	21 (12–40)	20 (12–40)
Vedolizumab dose interval				
Every 4 weeks	*N* (%)	3 (3.7%)	3 (5.7%)	6 (4.4%)
Every 6 weeks	*N* (%)	9 (11.0%)	11 (20.8%)	20 (14.8%)
Every 7 weeks	*N* (%)	3 (3.7%)	1 (1.9%)	4 (3.0%)
Every 8 weeks	*N* (%)	67 (81.7%)	37 (69.8%)	104 (77.0%)
Every 11 weeks	*N* (%)		1 (1.9%)	1 (0.7%)
Corticosteroid free clinical remission	*N* (%)	57/81 (70.4%)	35/49 (71.4%)	92/130 (70.9%)
Biochemical remission	*N* (%)	53/80 (66.3%)	41/51 (80.4%)	94/131 (71.8%)
Disease activity				
SCCAI-score	Median (IQR)		1 (1–2)	
HBI-score	Median (IQR)	3 (1–5)		
CRP (mg/L)	Median (IQR)	2.1 (1.0–4.0)	2.0 (1.0–4.1)	2.1 (1.0–4.0)
Faecal calprotectin (mg/kg)	Median (IQR)	58 (17–157)	32 (15–69)	45 (17–136)
Medical history				
Disease location UCa				
Proctitis	*N* (%)		2 (3.8%)	
Leftsided colitis	*N* (%)		21 (39.6%)	
Pancolitis	*N* (%)		30 (56.6%)	
Disease location CD				
Ileal	*N* (%)	26 (31.7%)		
Colonic	*N* (%)	26 (31.7%)		
Ileocolonic	*N* (%)	30 (36.6%)		
Additional upper GI disease	*N* (%)	7 (8.5%)		
Behaviour CD				
Inflammatory	*N* (%)	48 (58.5%)		
Penetrating	*N* (%)	11 (13.4%)		
Stricturing	*N* (%)	21 (25.6%)		
Penetrating + stricturing	*N* (%)	2 (2.4%)		
Perianal	*N* (%)	18 (22%)		
Prior treatment				
Prior ≥ 1 biologic	*N* (%)	60 (73.2%)	42 (79.2%)	102 (75.6%)
Prior ≥ 2 biologic	*N* (%)	39 (47.6%)	26 (49.1%)	59 (43.7%)
Prior bowel resection	*N* (%)	42 (58.5%)	5 (9.4%)	47 (34.8%)
Concomitant treatment				
Oral prednisone	*N* (%)	2 (2.4%)	3 (5.7%)	5 (3.7%)
Budesonide (oral or enema)	*N* (%)	4 (4.9%)	4 (7.5%)	8 (5.9%)
Mesalazine	*N* (%)	1 (1.2%)	19 (35.8)	20 (14.8%)
Immunomodulators	*N* (%)	1 (1.2%)	2 (3.8%)	3 (2.2%)
Tofacitinib	*N* (%)	-	1 (1.9%)	1 (0.7%)

[a]Maximum extend in medical history. Clinical remission was defined by a SCCAI ≤ 2 in UC patients and a HBI ≤ 4 in CD patients, biochemical remission was defined as a C-reactive protein (CRP) ≤ 5 mg/L and/or faecal calprotectin ≤250 μg/g (FCP).

8–22) and 6 (IQR 5–10) weeks, respectively. Cumulative SC VDZ drug survival is depicted in Figure S1. Adverse events ($n = 9$) were the main reason for the discontinuation of SC VDZ treatment both in CD and UC (Table 2). After a median duration of 9 weeks (IQR 5–15) of SC VDZ treatment, these patients switched back to IV VDZ. No UC patients discontinued SC VDZ due to loss of response. Four out of 11 CD patients (36.4%) who discontinued SC VDZ, were discontinued due to loss of response after 8, 17, 22 and 23 weeks, and switched to another treatment. Only one of these 4 CD patients with loss of response was in biochemical remission when switching to SC VDZ and two other patients were in CSFR at baseline. Three of these four patients were on an 8-week IV VDZ dosing scheme and one patient received IV VDZ every 6 weeks before switching to SC VDZ therapy. Two CD and one UC patient stopped SC VDZ therapy due to fear of needles and switched back to IV VDZ. One patient had to discontinue SC VDZ therapy due to moving abroad and was censored in further analyses. Of the patients discontinuing SC VDZ, one patient received IV VDZ every 4 weeks, two patients every 6 weeks, one patient every 7 weeks, 12 patients every 8 weeks and one patient every 11 weeks prior to switching to SC VDZ. Additional clinical details on the patients who discontinued SC VDZ are shown in Table S2. We could not identify factors associated with VDZ discontinuation in a logistic regression analysis (Table S3). However, CSFR and a low HBI at baseline approached statistical significance (OR 0.41 [95% CI 0.14–1.15, $p = 0.09$] and OR 1.16 [0.98–1.37, p = 0.09], respectively). A multivariate analysis was not performed as no variable was significantly associated with drug discontinuation.

3.3 | Safety

In total, 59 adverse events and 13 infections in 42 patients were observed that were possibly- or probably-related to SC VDZ injections (Table 3). Twenty-seven patients (20.0%) experienced an adverse event that was probably-related to SC VDZ injections. These included injection site reactions (pain, erythema, or swelling, $n = 15$, 11.1%) and headache ($n = 4$, 3.0%). Thirty-two patients (23.7%)

TABLE 2 Discontinuation of subcutaneous vedolizumab treatment

	CD	UC
	***n* = 11 (13.4%)**	***n* = 5 (9.4%)**
Treatment duration—weeks, median (IQR)	18 (8–22)	6 (5–10)
Reason discontinuation, *n* (%)		
Adverse events	5 (45.5%)	4 (80%)
Fear of needles	2 (18.2%)	1 (20%)
Loss of response	4 (36.4%)	

TABLE 3 Subcutaneous vedolizumab-related adverse events

	72.9 patient-years
Mild infections	8 (11 per 100 patient-years)
Covid-19	2
Fever of unknown origin	2
Upper respiratory tract	1
Dermatomycosis	1
Lower respiratory tract	1
Gastrointestinal	1
Moderate infections	4 (5.5 per 100 patient-years)
Urinary tract	3
Gastrointestinal	1
Severe infections	1 (1.4 per 100 patient-years)
Gastrointestinal	1
Probably-related	27 (37.0 per 100 patient-years)
Injection site reaction	15
Headache	6
Skin	2
Dyspnoea	1
Injection phobia	1
Arthralgia	1
Vasovagal collapse	1
Possibly-related	32 (43.9 per 100 patient-years)
Skin	7
Musculoskeletal	5
Headache	4
Malaise	4
Fatigue	3
Gastrointestinal	2
Injection related	2
Eye complications	1
Increase asthma	1
Sore throat	1
Nausea	1
Other	1
Serious adverse events	4 (5.5 per 100 patient-year)
Exacerbation cystic fibrosis	1
Obstructed bowel anastomosis	1
Metastatic colon cancer	1
Pregnancy with caesarean section	1

Note: Number of adverse events during treatment with vedolizumab subcutaneous. Infections were classified as: mild infections: no antibiotics or antiviral medication; moderate infections: oral antibiotics or antiviral medication; severe infections: hospitalisation or intravenously administrated antibiotic or antiviral medication.

experienced an adverse event that was considered possibly-related to the SC VDZ injections. Four patients experienced a serious adverse event. These included: hospitalisation due to a complication of cystic fibrosis and one pre-existent anastomotic bowel obstruction, which was dilated per endoscopic procedure. One patient had a recurrence of colorectal cancer, which was unknown at the moment of the switch to SC VDZ. At the time of diagnosis, the cancer was metastasized. The fourth patient was pregnant and a caesarean section had to be performed whereafter the child was respiratory insufficient 2 days postpartum. In 12 patients, 13 infections occurred; 8 mild infections, and 4 moderate infections (three urinary tract infections and one gastrointestinal infection). One patient required hospitalisation due to a severe gastrointestinal infection.

3.4 | Effectiveness

CSFR rates and biochemical remission rates at week 12 and week 24 of both CD and UC patients are shown in Figure 1A. In CD patients, 57/81 (70.4%) and 53/80 (66.3%) were in CSFR and biochemical remission at the initiation of therapy, respectively. In UC patients, 35/49 (71.4%) and 41/51 (80.4%) were in CSFR and biochemical remission at the initiation of therapy, respectively. CSFR and biochemical remission rates of these patients are displayed in Figure 1B. Median HBI, SCCAI, CRP, and FCP levels remained stable during follow-up and were not significantly different compared to the baseline measurement (Table 4) and are displayed in a profile plot (Figure S2).

3.5 | Vedolizumab serum concentrations

At the initiation of SC VDZ therapy, VDZ serum concentrations were assessed in 119 patients out of 135 patients (88.1%). These were trough concentrations as well as drawn more closely after injection. Median VDZ serum concentrations were 19 μg/ml (IQR 11–24 μg/ml, Table 4). There was no significant difference between SC VDZ concentrations in CD and UC patients at weeks 12 and 24 ($p = 0.22$ and $p = 0.53$). After the switch to SC VDZ, 124 VDZ serum concentrations were assessed in 90 patients. Median VDZ serum concentrations were 31 μg/ml (IQR 25–40 μg/ml) and 37 μg/ml (IQR 29–45 μg/ml) after 12 and 24 weeks, respectively (Table 4). VDZ serum concentrations at week 12 of ≤25 μg/ml were associated with lower CSFR rates (Figure 2). Furthermore, VDZ serum concentrations of ≥40 μg/ml at week 12 were associated with higher biochemical remission rates. At week 24, VDZ serum concentrations of 37 μg/ml were associated with higher biochemical remission rates. There was no association between VDZ serum concentrations and CSFR rates at week 24 ($p = 0.133$). Furthermore, there was no association between VDZ serum concentrations and the risk of adverse events which were deemed probably-related to SC VDZ ($p = 0.59$) or infections ($p = 0.65$) when comparing quartiles of VDZ serum concentrations and the occurrence of adverse events in each quartile. Additionally, VDZ serum concentrations were also not associated with adverse events which were deemed probably-related to SC VDZ (OR: 1.02, 95% CI: 0.96–1.09, $p = 0.55$) and infections (OR: 1.02, 95% CI: 0.93–1.11, $p = 0.75$) in a logistic regression model.

3.6 | Optimization of SC vedolizumab therapy

SC VDZ interval was shortened to one injection every 1.5 weeks for two patients due to clinical symptoms at the end of the week two dosing interval. SC VDZ dose interval was extended from every other week to every 3 weeks for two patients due to urticarial skin lesions and upper respiratory symptoms. In one patient, SC VDZ treatment was extended to every 4 weeks because of arthralgia complaints. In all patients who extended the interval between SC VDZ injections due to adverse events, the severity of the adverse events decreased.

4 | DISCUSSION

This real-world cohort study assessed the drug survival, effectiveness, safety, and VDZ serum concentrations of SC VDZ maintenance treatment after switching from IV VDZ treatment. Eleven CD (13.4%) and five UC patients (9.4%) had to discontinue SC VDZ treatment (11.9% of total) after a median follow-up-up time of 27 weeks. Patients who discontinued treatment for adverse events or needle fear successfully switched back to IV VDZ therapy. In patients who continued SC VDZ treatment, clinical and biochemical disease activity remained stable compared to baseline (IV VDZ treatment for at least 4 months).

In the previous VISIBLE I and II trial (for CD and UC, respectively), the SC VDZ discontinuation rates were 27.4% and 38.9% within 52 weeks of treatment.[5,6] Twelve percent of our cohort discontinued SC VDZ (13.4% in CD patients and 9.4% in UC patients). However, the results of our study, with a median follow-up of 27 weeks, are not directly comparable to the VISIBLE trial. In these trials, patients switched to SC VDZ directly after they experienced a clinical response to two infusions of VDZ. Up to now, two smaller real-world cohorts have described the discontinuation rate of SC VDZ. An English cohort study reported that 8% of patients stopped SC VDZ therapy within 12 weeks, which is comparable to our cohort.[18] However, in a Danish study, only 4.5% and 12.5% of patients discontinued SC VDZ after 6 and 12 months, respectively.[18,19]

Several previous real-world studies described the discontinuation rate of long-term follow-up IV VDZ therapy.[20–22] The discontinuation rates of the current study (13.4% CD and 9.4% UC), with a median follow-up of approximately half a year, seemed to be higher compared to a Dutch ICC registry study. In that study, the discontinuation rate of IV VDZ between 52 and 104 weeks after IV VDZ

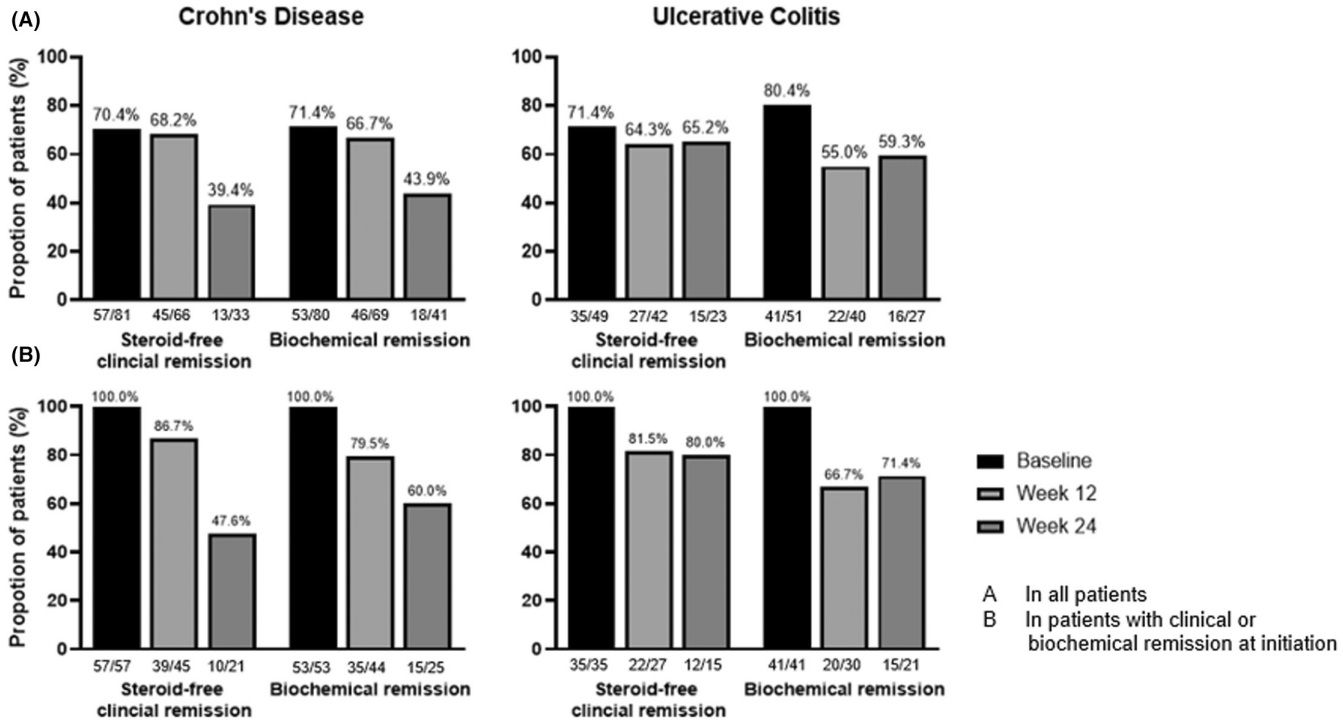

FIGURE 1 Corticosteroid-free clinical and biochemical remission rates at weeks 12 and 24. Clinical remission was defined by SCCAI ≤ 2 in UC patients and HBI ≤ 4 in CD patients. Biochemical remission was defined as C-reactive protein (CRP) ≤ 5 mg/L and/or faecal calprotectin ≤250 µg/g (FCP).

TABLE 4 Clinical and biochemical effectiveness and vedolizumab serum concentrations

	Baseline	*n*	Week 12	*n*	Week 24	*n*
All patients						
CRP, mg/L, median (IQR)	2.1 (1.0–4.0)	130	2.7 (1.1–5.0)	97	2.0 (1.3–5.0)	52
FCP, mg/kg, median (IQR)	45 (17–136)	104	49 (173–19)	87	70 (19–181)	36
VDZ concentration, µg/ml, median (IQR)[a]	19 (11–24)	119	31 (25–40)**	81	37 (29–45)**	34
VDZ trough concentration, µg/ml, median (IQR)[b]	19 (11–24)	119	27 (20–32)**	34	36 (29–39)**	8
Crohn's disease						
HBI (IQR)	3 (1–5)	81	3 (1–4)	60	2 (1–6)	23
CRP, mg/L, median (IQR)	2.1 (1.0–4.0)	79	2.6 (1.1–5.0)	62	2.1 (1.4–4.3)	31
FCP, mg/kg, median (IQR)	58 (17–157)	66	44 (20–174)	60	112 (27–387)	21
VDZ concentration, µg/ml, median (IQR)[a]	19 (11–25)	74	32 (25–44)**	55	37 (31–49)**	21
VDZ trough concentration, µg/ml, median (IQR)[b]	19 (11–25)	74	27 (20–32)**	23	34 (28–38)	3
Ulcerative colitis						
SCCAI (IQR)	1 (1–2)	49	1 (1–2)	35	1 (0.75–2)	18
CRP, mg/L, median (IQR)	2.0 (1.0–4.1)	51	2.7 (1.0–4.7)	35	1.9 (0.9–6.0)	21
FCP, mg/kg, median IQR	32 (15–69)	38	54 (17–156)	27	35 (15–133)	15
VDZ concentration, µg/ml, median (IQR)[a]	19 (11–23)	45	31 (26–35)**	26	38 (28–42)**	13
VDZ trough concentration, µg/ml, median (IQR)[b]	19 (11–23)	45	27 (19–32)**	11	38 (29–40)*	5

[a]serum concentration measured at random timepoint.

[b]trough concnentration measured 12 to 21 days after SC injection.

*p-value: <0.05.; **p-value: <0.005 using pairwise Wilcoxon signed rank test.

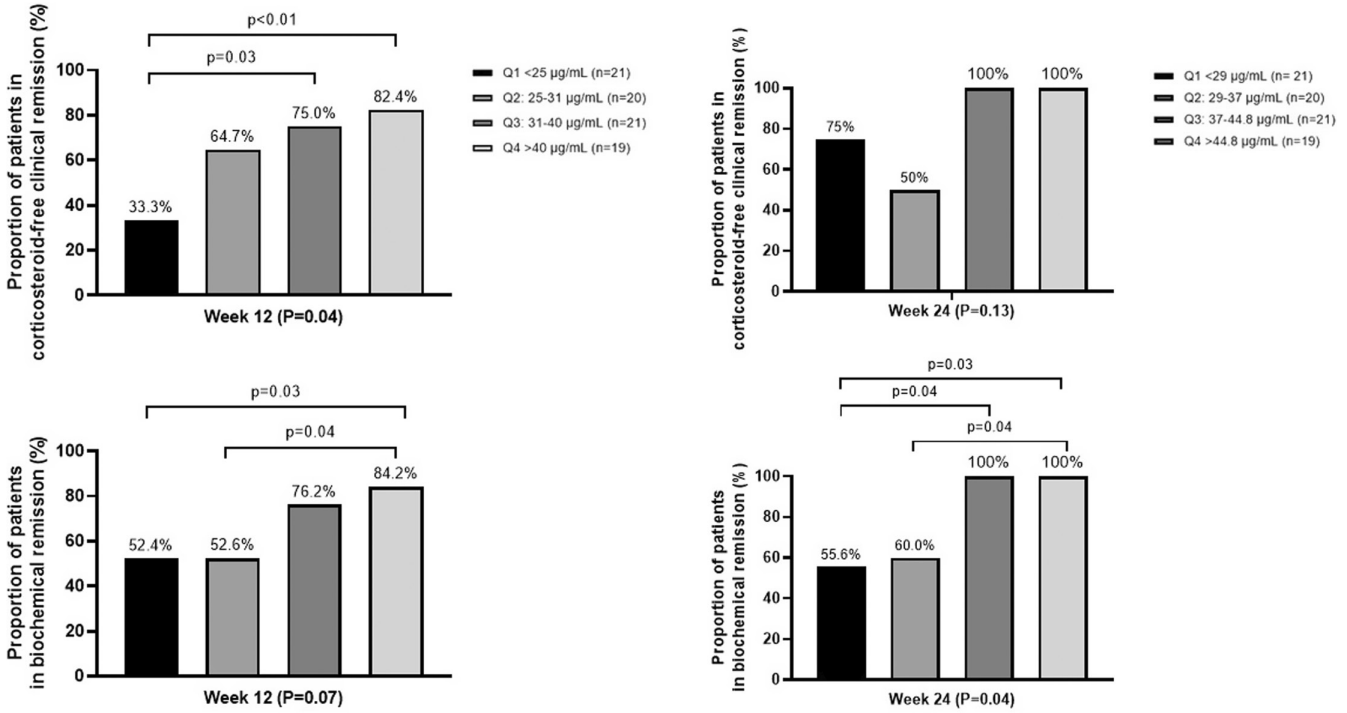

FIGURE 2 Quartile analysis depicting the exposure-response relationship between vedolizumab serum concentrations and clinical and biochemical remission rates. Clinical remission was defined by SCCAI ≤ 2 in UC patients and HBI ≤ 4 in CD patients. Biological remission was defined as C-reactive protein (CRP) ≤ 5 mg/L and/or faecal calprotectin (FCP) ≤ 250 mg/kg.

initiation was 16% for CD and 10% for UC. Similar to our study, more CD patients discontinued VDZ compared to UC patients. A French cohort reported discontinuation rates for 1, 2, and 3 years after IV VDZ initiation. Of all patients who still used IV VDZ after 1 year of treatment, 35.4% and 48.8% of CD patients and 20.8% and 36.1% of UC patients had discontinued IV VDZ 1 and 2 years later, respectively. Lastly, in a Danish cohort on IV VDZ, between 1 and 2 years after IV VDZ treatment initiation, 7.9% of CD and 3.3% of UC patients had discontinued IV VDZ. Thus, the SC VDZ discontinuation rate in the current study seemed to be higher than the English and Danish long-term IV VDZ cohorts and similar to the French cohort.

The difference in discontinuation rate in the current study compared to previous literature is mainly explained by a higher rate of discontinuation due to adverse events. The number of patients withdrawing from SC VDZ therapy due to adverse events in our cohort (6.1% CD and 7.5% UC) was higher compared to the VISIBLE trials (4% CD and 4.7% UC) but comparable to the real-world English cohort (6.5%).[5,6,18] Only four of 82 CD patients (4.9%) and no UC patients discontinued therapy due to loss of response in our cohort. In the VISIBLE trials, more CD patients discontinued therapy due to loss of response compared to UC patients (28.4% and 17%, respectively). The differences in discontinuation rate may be explained by our short follow-up duration and the fact that patients in this study were all on maintenance IV VDZ at the moment of switching. The number of patients experiencing injection-site reactions in the VISIBLE I trial (10.4%) was comparable to our cohort. The number of patients experiencing injection site reactions in the VISIBLE II trial was only 2.9%. In addition, in the VISIBLE II trial, 9.0% of patients experienced hypersensitivity-related AE's, which was not observed in our cohort.

The VISIBLE trials reported CSFR rates of 48% and 46% in CD and UC patients, respectively, at week 52 after switching to SC VDZ treatment.[5,6] In the current study, CSFR rates at week 12 and 24 weeks were higher for UC patients and similar to CD, when comparing with the VISIBLE trials. Remission rates remained stable in UC patients. In CD patients, the CSFR rate dropped for CD patients between 12 and 24 weeks from 68.2% to 39.4% of patients. This drop might partly be explained by the relatively low number of CD patients who had a week 24 visit. Also, as more CD patients had discontinued SC VDZ and were, therefore, considered not in CSFR, the week 24 CSFR rate of CD became lower. Hence, the CSFR rates might be an underestimation and may explain the drop in CSFR in CD patients at week 24.

Median VDZ serum concentrations in our study (31 µg/ml [25–40] at week 12 and 37 µg/ml [29–44.8] at week 24) were comparable to median VDZ trough concentrations in the VISIBLE studies (34.6 µg/ml [90% CI, 15.5–72.8 µg/ml] in UC and 30.2 µg/ml [minimum to maximum, 0.78–70.1 µg/ml] in CD patients). VDZ serum concentrations were high compared to the serum trough concentrations described in the English real-world cohort assessing SC VDZ effectiveness up to 12 weeks.[18] These observations raise the question of whether SC VDZ injection dose intervals should be extended. The

current study found no association between adverse events and higher VDZ serum concentrations.

This is the third real-world study to evaluate the effectiveness and safety of switching from IV to SC VDZ maintenance treatment in IBD patients. The current study has a longer follow-up time than the British cohort and included more patients than the British and Danish study.[18] Furthermore, the strength of this study lies in the systematic prospective follow-up with pre-defined clinically relevant endpoints and the substantial cohort size. Due to the participation of both academic and non-academic hospitals and the patient characteristics of our cohort (mostly anti-TNF experienced), our data reflects a daily practice that justifies generalizability. However, most patients were included in tertiary centres, which may lead to a more refractory population.

One of the limitations of our study is that clinical disease assessment and laboratory tests were not performed during each visit to each participant. These missing data might not be at random as treating physicians probably do not always perform laboratory tests when a patient is in CSFR, which can lead to underestimating remission rates. Second, there was no comparator arm in this study as this was a descriptive cohort study and results were compared with baseline measurements (based on IV VDZ treatment). To reduce bias, we included patients with an intensified IV VDZ dose interval, patients with biochemical or clinical disease activity, and concomitant corticosteroids. As patients had to be willing to switch to SC VDZ, there is a potential risk for bias as more therapy refractory patients might be less willing to switch to the SC formulation. Third, we did not assess endoscopic outcomes. As the majority was in both clinical and biochemical remission at the initiation of SC VDZ, endoscopic disease activity was assessed only in a few patients at the moment of switching. Also, only a couple of patients underwent endoscopy during follow-up as most patients maintained clinical and biochemical remission. Presenting the endoscopic outcomes might lead to bias as this was probably primarily performed in patients if non-invasive biomarkers were inconclusive. Lastly, the follow-up period is relatively short to evaluate the long-term safety profile.

In conclusion, clinical and biochemical disease activity remained stable after switching from IV VDZ to SC VDZ. However, a proportion of patients had to switch back from SC VDZ to IV VDZ due to injection-related side effects or needle fear. Adverse events did not seem to relate to higher VDZ serum concentrations. As VDZ serum concentrations significantly increased after switching to SC VDZ, dose interval extension may be an interesting topic for future research. Further studies are needed to confirm the long-term effectiveness and safety of SC VDZ therapy.

AUTHOR CONTRIBUTIONS

Adriaan Volkers: Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); visualization (equal); writing – original draft (equal). **Tessa Straatmijer:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); validation (equal); visualization (equal); writing – original draft (equal). **Marjolijn Duijvestein:** Supervision (equal); writing – review and editing (equal). **Amber Sales:** Data curation (equal); investigation (equal); project administration (equal). **Amit Levran:** Data curation (equal); project administration (equal). **Fiona D.M. van Schaik:** Resources (equal); writing – original draft (equal). **P.W.J. Maljaars:** Resources (equal); writing – review and editing (equal). **Krisztina B Gecse:** Resources (equal); writing – review and editing (equal). **Cyriel Ponsioen:** Resources (equal); writing – review and editing (equal). **Joep Grootjans:** Writing – original draft (equal). **Jurij Hanzel:** Resources (equal); writing – review and editing (equal). **Greetje Tack:** Resources (equal); writing – review and editing (equal). **Jeroen M Jansen:** Resources (equal); writing – review and editing (equal). **Frank Hoentjen:** Resources (equal); writing – review and editing (equal). **Nanne de Boer:** Resources (equal); writing – review and editing (equal). **Sander van der Marel:** Resources (equal); writing – review and editing (equal). **Gerard Dijkstra:** Resources (equal); writing – review and editing (equal). **Bas Oldenburg:** Resources (equal); writing – original draft (equal). **Mark Löwenberg:** Resources (equal); supervision (equal); writing – review and editing (equal). **Andrea E. van der Meulen-de Jong:** Conceptualization (equal); methodology (equal); resources (equal); supervision (equal); writing – review and editing (equal). **Geert D'Haens:** Conceptualization (equal); methodology (equal); resources (equal); supervision (equal); writing – review and editing (equal).

ACKNOWLEDGEMENTS

We thank the patients and research team for their participation and cooperation in this study.

FUNDING INFORMATION

The ICC fellow [T.S.] is sponsored by AbbVie, Pfizer, Takeda, Celgene, Janssen Pharmaceutica, Teva Pharmaceutical Industries, MLDS, Cablon Medical, Ferring pharmaceuticals, Mundipharma, Dr. Falk Pharma, Sandoz and Tramedico.

CONFLICT OF INTEREST

A.V., T.S., A.S., A.L.: none. M.D.: reports advisory fees from Echo Pharma and Robarts Clinical Trials, Inc., speaker fees from Janssen, Merck & Co., Inc., Pfizer, Takeda and Tillotts Pharma, and nonfinancial support from Dr. Falk Pharm. F.S: Advisory Boards Takeda, Galapagos. K.G.: has received grants from Pfizer Inc. and Celltrion; consultancy fees from AbbVie, Arena Pharmaceuticals, Galapagos, Gilead, ImmunicTherapeutics, Janssen Pharmaceuticals, Novartis, Pfizer Inc., Samsung Bioepis and Takeda; and speaker's honoraria from Celltrion, Ferring, Janssen Pharmaceuticals, Novartis, Pfizer Inc., Samsung Bioepis, Takeda and Tillotts. C.P.: received grants or contracts from Takeda, Pliant, and Gilead Sciences; consulting fees from Pliant and Shire (Takeda); and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Takeda, Tillotts Pharma, and Pfizer outside of the submitted work. J.G.: has served as a speaker for: Dr. Falk,

GlaxoSmithKline, Janssen-Cilag. J.H.: speaker's fees from Abbvie, Janssen, Takeda; consulting fees from Alimentiv Inc. G.T.: none. J.J.: has served on advisory boards and as a speaker or consultant for Abbvie, Amgen, Ferring, Fresenius, Janssen, MSD, Pfizer, Takeda. A.G.L. F.H.: Frank Hoentjen has served on advisory boards and as a speaker for Abbvie, Janssen-Cilag, MSD, Takeda, Celltrion, Teva, Sandoz and Dr Falk Funding (Grants/Honoraria): Takeda, Janssen-Cilag, Abbvie Consulting Fees: Celgene. N.B.: has served as a speaker for AbbVie and MSD and has served as a consultant and/or principal investigator for TEVA Pharma BV and Takeda. He has received a [unrestricted] research grant from Dr. Falk, TEVA Pharma BV, MLDS and Takeda. All outside the submitted work. G.Dijkstra.: has received speakers fees from Janssen-Cilag, Pfizer, Takeda and Abbvie. B.O.: has served as speaker for Galapagos, MSD, Janssen and received unrestricted grants from Takeda, Pfizer, Galapagos, Ferring, Celltrion and Abbvie. M.L.: has served as a speaker and/or principal investigator for: Abbvie, Alimentiv, Bristol Myers Squibb, Celgene, Covidien, Dr. Falk, Ferring Pharmaceuticals, Galapagos, Gilead, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, Pfizer, Protagonist therapeutics, Receptos, Takeda, Tillotts, Tramedico. He has received research grants from AbbVie, Merck Sharp & Dohme, Dr Falk, Achmea healthcare, Galapagos and ZonMW. A.M.: has served as speaker for: Galapagos, Janssen-Cilag, Takeda, Tramedico. She has received research grants from Cablon, Galapagos, Nestle, Norgine and ZonMW. G.D.: Consultancy for Abbvie, Agomab, AstraZeneca, AM Pharma, AMT, Arena Pharmaceuticals, Bristol Meiers Squibb, Boehringer Ingelheim, Celltrion, Eli Lilly, Exeliom Biosciences, Exo Biologics, Galapagos, Index Pharmaceuticals, Kaleido, Roche, Gilead, Glaxo Smith Kline, Gossamerbio, Pfizer, Immunic, Johnson and Johnson, Origo, Polpharma, Procise Diagnostics, Prometheus laboratories, Prometheus Biosciences, Progenity, Protagonist. Speaker's bureau for Abbvie, Arena, Galapagos, Gilead, Pfizer, BMS, Takeda.

MANUSCRIPT STATEMENT

This study has been presented at the Digestive Disease Days in 2021 and ECCO 2022 as an oral presentation and at the UEG Week 2021. The manuscript, including figures and tables, has not been previously published and is not under consideration elsewhere.

ORCID

Adriaan Volkers https://orcid.org/0000-0002-9547-1627
Tessa Straatmijer https://orcid.org/0000-0001-6989-5226
Jeroen Maljaars https://orcid.org/0000-0003-0477-9499
Jurij Hanzel https://orcid.org/0000-0003-3158-8014
Frank Hoentjen https://orcid.org/0000-0001-5314-4452

REFERENCES

1. Wyant T, Fedyk E, Abhyankar B. An overview of the mechanism of action of the monoclonal antibody vedolizumab. J Crohns Colitis. 2016;10:1437–44.
2. Zeissig S, Rosati E, Dowds CM, Aden K, Bethge J, Schulte B, et al. Vedolizumab is associated with changes in innate rather than adaptive immunity in patients with inflammatory bowel disease. Gut. 2019;68:25–39.
3. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369:711–21.
4. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369:699–710.
5. Sandborn WJ, Baert F, Danese S, Krznarić Ž, Kobayashi T, Yao X, et al. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis. Gastroenterol. 2020;158:562–572.e12.
6. Vermeire S, D'Haens G, Baert F, Danese S, Kobayashi T, Loftus EV, 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.
7. Bittner B, Richter W, Schmidt J. Subcutaneous Administration of Biotherapeutics: an overview of current challenges and opportunities. BioDrugs. 2018;32:425–40.
8. Richter WF, Jacobsen B. Subcutaneous absorption of biotherapeutics: knowns and unknowns. Drug Metab Dispos. 2014;42:1881–9.
9. Dreesen E, Verstockt B, Bian S, de Bruyn M, Compernolle G, Tops S, et al. Evidence to support monitoring of vedolizumab trough concentrations in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2018;16:1937–1946.e8.
10. Ungaro RC, Yarur A, Jossen J, Phan BL, Chefitz E, Sehgal P, et al. Higher trough vedolizumab concentrations during maintenance therapy are associated with corticosteroid-free remission in inflammatory bowel disease. J Crohns Colitis. 2019;13:963–9.
11. Löwenberg M, Vermeire S, Mostafavi N, Hoentjen F, Franchimont D, Bossuyt P, et al. Vedolizumab induces endoscopic and histologic remission in patients with Crohn's disease. Gastroenterology. 2019;157:997–1006.e6.
12. Pouillon L, Rousseau H, Busby-Venner H, de Carvalho Bittencourt M, Choukour M, Gauchotte G, et al. Vedolizumab trough levels and histological healing during maintenance therapy in ulcerative colitis. J Crohns Colitis. 2019;13:970–5.
13. Vavricka SR, Bentele N, Scharl M, Rogler G, Zeitz J, Frei P, et al. Systematic assessment of factors influencing preferences of Crohn's disease patients in selecting an anti-tumor necrosis factor agent (CHOOSE TNF TRIAL). Inflamm Bowel Dis. 2012;18:1523–30.
14. Allen PB, Lindsay H, Tham TC. How do patients with inflammatory bowel disease want their biological therapy administered? BMC Gastroenterol. 2010;10:1.
15. Cronin J, Moore S, Lenihan N, O'Shea M, Woods N. The non-drug costs associated with the administration of an intravenous biologic treatment in the hospital setting. Ir J Med Sci. 2019;188:821–34.
16. Viola M, Sequeira J, Seiça R, Veiga F, Serra J, Santos AC, et al. Subcutaneous delivery of monoclonal antibodies: how do we get there? J Control Release. 2018;286:301–14.
17. Salbato J, Parnell J, Reddy R, Christie R, Lockton S, Hauenstein S, et al. Validation of a Homogenous Mobility Shift Assay (HSMA) for the Measurement of Golimumab (GLM) and Antibodies to Golimumab (ATG) in Inflammatory Bowel Disease (IBD) Patient Serum: 1794. Official Journal of the American College of Gastroenterology. 2013;108:S540–1.
18. Ventress E, Young D, Rahmany S, Harris C, Bettey M, Smith T, et al. Transitioning from intRavenous to subcutAneous VEdolizumab in patients with infLammatory bowEl diSeaSe (TRAVELESS). J Crohns Colitis. 2021;16:911–21.
19. 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;55:1389–401.

20. Biemans VBC, van der Woude CJ, Dijkstra G, Dijkstra G, van der Meulen-de Jong AE, Oldenburg B, et al. Vedolizumab for inflammatory bowel disease: two-year results of the initiative on Crohn and colitis (ICC) registry, a Nationwide prospective observational cohort study: ICC registry - vedolizumab. Clin Pharmacol Ther. 2020;107:1189–99.
21. Amiot A, Serrero M, Peyrin-Biroulet L, Filippi J, Pariente B, Roblin X, et al. Three-year effectiveness and safety of vedolizumab therapy for inflammatory bowel disease: a prospective multi-centre cohort study. Aliment Pharmacol Ther. 2019;50:40–53.
22. Eriksson C, Marsal J, Bergemalm D, Vigren L, Björk J, Eberhardson M, et al. Long-term effectiveness of vedolizumab in inflammatory bowel disease: a national study based on the Swedish National Quality Registry for inflammatory bowel disease (SWIBREG). Scand J Gastroenterol. 2017;52:722–9.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Volkers A, Straatmijer T, Duijvestein M, Sales A, Levran A, van Schaik F, 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. https://doi.org/10.1111/apt.17153