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An Objective Comparison of Vedolizumab and Ustekinumab Effectiveness in Crohn's Disease Patients' Failure to TNF-Alpha Inhibitors

Sara Onali, MD, PhD[1,2], Daniela Pugliese, MD, PhD[3], Flavio Andrea Caprioli, MD, PhD[4,5], Ambrogio Orlando, MD[6], Livia Biancone, MD, PhD[7], Olga Maria Nardone, MD[8], Nicola Imperatore, MD[9], Gionata Fiorino, MD, PhD[10], Maria Cappello, MD[11], Anna Viola, MD[12], Maria Beatrice Principi, MD, PhD[13], Cristina Bezzio, MD[14], Annalisa Aratari, MD[15], Sonia Carparelli, MD[16], Silvia Mazzuoli, MD[17], Francesco Manguso, MD, PhD[9], Laurino Grossi, MD, PhD[18], Giorgia Bodini, MD, PhD[19], Davide Ribaldone, MD[20], Giammarco Mocci, MD[21], Agnese Miranda, MD[22], Luigi Minerba, MD, PhD[1,2], Agnese Favale, MD[1,2], Mauro Grova, MD[6], Ludovica Scucchi, MD[7], Simone Segato, MD[23,24], Walter Fries, MD, PhD[12], Fabiana Castiglione, MD, PhD[8], Alessandro Armuzzi, MD, PhD[25,26] and Massimo C. Fantini, MD, PhD[1,2], on behalf of the IG-IBD

INTRODUCTION: **The use of ustekinumab and vedolizumab as second-line therapies in patients with Crohn's disease (CD) in which tumour necrosis factor alpha inhibitors (TNFi) failed is still debated. The aim of this study was to compare, in a large multicenter observational retrospective cohort, the effectiveness of ustekinumab and vedolizumab as second-line therapies, as assessed by clinical and objective outcomes including endoscopy and gastrointestinal imaging.**

METHODS: **Clinical response, remission, and steroid-free remission at weeks 26 and 52 were evaluated in a retrospective propensity score–weighted and propensity score–matched cohort of patients in which TNFi failed. Objective response and remission were evaluated by 1 or more techniques among endoscopy, magnetic resonance/computed tomography enteroclysis, and small bowel ultrasound.**

RESULTS: **A total of 470 patients with CD (239 treated with ustekinumab and 231 treated with vedolizumab) were included in the study. At week 26, clinical outcomes were similar between the 2 groups. At week 52, clinical remission (ustekinumab 42.5% vs vedolizumab 55.5%, $P = 0.01$) and steroid-free remission (ustekinumab 40.6% vs vedolizumab 51.1%, $P = 0.038$) rates were significantly higher in vedolizumab-treated patients. Three hundred two patients (hundred thirty-five treated with ustekinumab and hundred sixty-seven treated with vedolizumab) had an objective evaluation of disease activity at baseline and week 52. At week 52, objective response and remission rates were similar between the 2 groups. Clinical response at week 26 predicted steroid-free remission at week 52 in both ustekinumab-treated and vedolizumab-treated patients. Safety profiles were similar between the 2 groups.**

[1]Departement of Medical Science and Public Health, Gastroenterology Unit, University of Cagliari, Cagliari, Italy; [2]Gastroenterology Unit, Azienda Ospedaliero-Universitaria (AOU) di Cagliari, Cagliari, Italy; [3]CEMAD, IBD UNIT, Unità Operativa Complessa di Medicina Interna e Gastroenterologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy; [4]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy; [5]Gastroenterology and Endoscopy Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico di Milano, Milan, Italy; [6]IBD UNIT "Villa Sofia Cervello" Hospital, Palermo, Italy; [7]Department of Systems Medicine, University of Rome "Tor Vergata," Rome, Italy; [8]Gastroenterology, Department of Clinical Medicine and Surgery, AOU Federico II Napoli, Napoli, Italy; [9]Gastroenterology and Endoscopy Unit, AORN A. Cardarelli of Naples, Naples, Italy; [10]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; [11]IBD Clinic, Gastroenterology Section, Promise, University of Palermo, Sicily, Italy; [12]IBD-Unit, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [13]Gastroenterology Section (D.E.T.O.), Policlinico-Università Bari, Bari, Italy; [14]Gastroenterology Unit, Asst Rhodense, Rho, Milan, Italy; [15]UOS IBD, Ospedale San Filippo Neri, Rome, Italy; [16]UOC di Gastroenterologia ed Endoscopia Digestiva, Fondazione Casa Sollievo della Sofferenza, IRCCS, San Giovanni Rotondo, Italy; [17]UOC di Gastroenterologia, Ospedale "Mons Raffaele Dimiccoli," Barletta, Italy; [18]G d'Annunzio University DSMOB, Gastroenterology Unit Ospedale Spirito Santo Pescara, Pescara, Italy; [19]Policlinico San Martino, Università degli studi di Genova, Gastroenterology Units, Genova, Italy; [20]Dipartimento di Scienze Mediche, Università degli Studi di Torino, Turin, Italy; [21]Gastroenterologia ARNAS G. Brotzu, Cagliari, Italy; [22]Gastroenterology and Endoscopy Unit, University of Campania"L. Vanvitelli," Naples, Italy; and [23]Gastroenterology and Endoscopy Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico di Milano, Italy. [24]Current address: Gastroenterologia ed Endoscopia Digestiva, Ospedale di Circolo e Fondazione Macchi, Varese, Italy; [25]IBD Center, IRCCS Humnanitas Research Hospital, Rozzano, Milan Italy; and [26]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy. **Correspondence:** Massimo C. Fantini, MD, PhD. E-mail: massimoc.fantini@unica.it.

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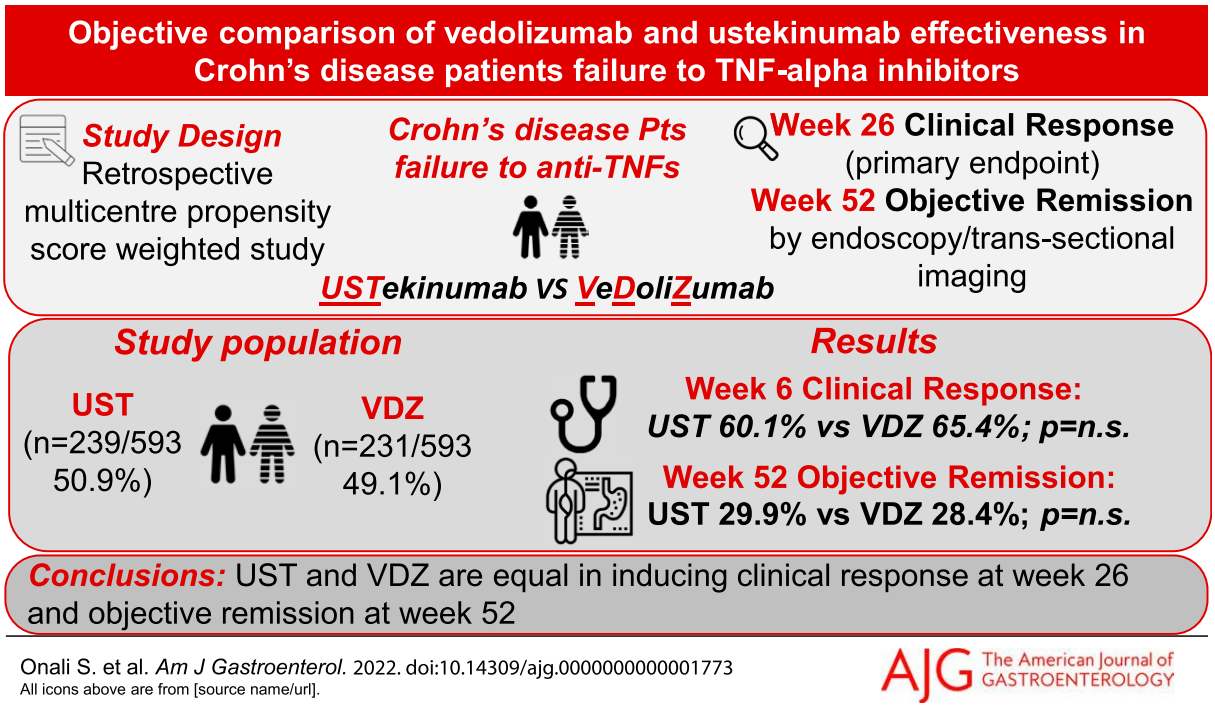

DISCUSSION: **In patients with CD in which TNFi failed, both ustekinumab and vedolizumab showed similar clinical effectiveness after 26 weeks of treatment. At 1 year, vedolizumab was associated with a higher rate of clinical remission when compared with ustekinumab. However, no difference was observed between the 2 groups when objective outcomes were investigated at this time point.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C489, http://links.lww.com/AJG/C490, http://links.lww.com/AJG/C491, http://links.lww.com/AJG/C492, http://links.lww.com/AJG/C493, http://links.lww.com/AJG/C494, http://links.lww.com/AJG/C495, http://links.lww.com/AJG/C496

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INTRODUCTION

Crohn's disease (CD), one of the major forms of inflammatory bowel disease (IBD), is a chronic inflammatory disorder of the gut characterized by the progressive accumulation of organ damage (e.g., abscess, fistulas, and stenosis) (1).

In the past decade, the clinical management of CD has evolved, and the use of biological therapies, aimed at prevent intestinal damage, has considerably increased (2,3). Tumor necrosis factor alpha inhibitors (TNFi) are monoclonal antibodies considered the first-line biologic therapy for the management of moderate-to-severe CD refractory to conventional therapy (4). Despite an overall excellent efficacy, approximately one-third of patients do not respond to induction therapy, and among responders, up to 45% will progressively lose response over the time (5–7).

Recently, several new therapies, including the anti-integrin alpha-4/beta-7 vedolizumab (VDZ) and the anti-p40 IL12/IL23 ustekinumab (UST) have been approved for the treatment of moderate-to-severe CD (8,9). The different modes of action of UST and VDZ, variable efficacy and safety profiles, respectively, pose the question about the choice between them after TNFi-based treatment. In the absence of prospective, randomized head-to-head trials, retrospective real-world studies have been conducted in limited number of patients with CD reporting conflicting data (10–14). In the attempt to pool these data, a recent meta-analysis showed no difference in steroid-free remission between UST and VDZ at the end of the induction, while UST proved to be superior after 1 year of treatment (odds ratio [OR] 1.56, 95% confidence interval [CI] 1.23–1.97) (15). However, no comparative data using objective outcomes have been reported. To address this issue, we performed a retrospective, multicenter, real-world study comparing the effectiveness of UST and VDZ in patients with active CD in which 1 or more TNFi failed. In this study, the effectiveness of VDZ vs UST was evaluated by endoscopy and/or cross-sectional imaging in addition to clinical, serologic, and fecal parameters.

METHODS

Study design and setting

This was a retrospective, observational, real-world, multicenter, cohort study involving 20 Italian IBD referral centers on behalf of the Italian Group for the study of Inflammatory Bowel Disease. Patients with CD, previously treated with TNFi, who received a second-line therapy with either UST or VDZ according to clinical standard of care (16), were considered for inclusion in the study.

Demographic data including sex, age, smoking status, and disease-related characteristics such as age at diagnosis, disease location and behavior by Montreal Classification for CD (17), previous and concurrent CD-related treatments, previous TNFi, including data on primary/secondary failure and intolerance

status and previous surgery, were extracted from patients' clinical records and collected in a common database.

Data on disease activity, calculated by the Harvey-Bradshaw Index (HBI) at baseline and at weeks 26 and 52 (±3 weeks), were recorded. Ileocolonoscopy and/or magnetic resonance/computed tomography (MR/CT) enteroclysis and/or small bowel ultrasound performed within 3 months before the beginning of the treatment and at 1 year of therapy (±3 months) were considered for objective evaluation if data from at least one of the diagnostic procedures were available at both baseline and week 52. Fecal calprotectin (FC) and C-reactive protein (CRP) levels at baseline and at weeks 26 and 52 were recorded, when available. Side effects and adverse events (AEs) reported in the clinical records were also collected.

Participants

Eligible patients had to have a confirmed diagnosis of CD for at least 3 months, show failure (primary or secondary) or be intolerant to 1 or more TNFi according to the current European Crohn's and Colitis Organization guidelines (4), and have an indication to a second biological therapy with either VDZ or UST for luminal disease. Clinical conditions recorded at the start of either VDZ or UST were considered as baseline conditions. At baseline, enrolled patients had to have active disease as defined by an HBI ≥5. Patients with missing or incomplete demographic data at baseline or insufficient clinical data precluding HBI calculation at baseline and 26 weeks (±3 weeks) of treatment were not eligible. After week 26, the last-observation carried forward method was adopted to impute the missing HBI at week 52. Patients with missing objective evaluation at baseline or after 1 year of treatment were included in the overall population for the analysis of clinical outcomes but removed from the objective evaluation analysis.

UST was administered 6 mg/kg intravenously (IV) in the induction, followed by maintenance with UST 90 mg subcutaneously every 12 or 8 weeks, and VDZ was administered 300 mg IV at 0, 2, and 6 weeks for the induction and every 8 or 4 weeks as maintenance, according to standard practice.

Outcomes

The primary outcome of this study was clinical response at week 26, defined as the reduction of HBI ≥3 points when compared with the baseline or HBI <5 if HBI ≤7 at baseline. Secondary outcomes were clinical response at week 52 and clinical remission and steroid-free clinical remission (SFR) at week 26 and week 52, defined by an HBI ≤4 alone or HBI ≤4 with or without concomitant steroids, respectively. Objective response and objective remission were defined based on results obtained from at least 1 among endoscopy, bowel ultrasound, and CT or MR enteroclysis at week 52. Endoscopic response was defined as the improvement of mucosal inflammation and the absence of deep ulcerations when compared with those at baseline. Endoscopic remission was defined as normalization of the intestinal mucosa, except for persistence of sporadic aphtoid ulcers. Ultrasound response was defined as reduction of bowel wall thickness (BWT) when compared with that at baseline. Ultrasound remission was considered as a normal BWT (≤3 mm for the small bowel and ≤4 mm for the colon) and the absence of any complication detectable with this method. Radiologic response was defined by improvement of BWT and of inflammatory fat, mural blood flow, and hyperenhancement compared with baseline imaging. Radiologic remission was defined by complete normalization of inflammatory parameters on CT or MR enteroclysis. In case of CD localized both in the small bowel and in the colon, the main affected region was considered to evaluate objective outcomes.

Statistical methods

Standard descriptive statistic was used to analyze patient characteristics. Continuous variables were described as medians and interquartile ranges (IQR). Categorical variables were described as number of cases and proportions. Comparisons between variables were performed by the χ^2 and Mann-Whitney U tests.

To minimize the effect of confounding variables, propensity score with inverse probability of treatment weighting (IPTW) was used in the main analysis. Potential confounding variables considered for propensity score calculation were age, age at diagnosis, sex, smoking habit, disease location and behavior by Montreal classification, proximal gastrointestinal disease, perianal disease, use of immunosuppressant and steroids at baseline, disease activity at baseline by the HBI, extraintestinal manifestations, previous anti-TNF exposure, and reason for anti-TNF discontinuation. Results from IPTW analysis were replicated by using propensity score matching as sensitivity analysis (see Supplementary Methods, Supplementary Digital Content 1, http://links.lww.com/AJG/C489).

Two previous real-world studies investigating clinical and objective responses in 2 independent cohorts of relatively unselected patients with CD treated with either UST or VDZ as second-line therapies after TNFi treatment (18,19). Despite the different response rates showed by UST and VDZ, clinical and objective responses within the same treatment group were not significantly different by 6 months of treatment. To catch clinical response at a time point more likely mirroring objective response, 6 months after treatment start was chosen as the primary evaluation time point. Therefore, to catch a significant difference ($P < 0.05$) assuming a 6-month response rate of 76% among patients treated with VDZ and 60% among patients treated with UST as previously published, a sample size of 270 patients (135 patients treated with VDZ vs 135 treated with UST) was considered adequate to obtain a study power of 80%. Statistical analysis was performed by STATA 16.1 (StataCorp, College Station, TX).

Ethical considerations

The study was approved by the Ethics Committee of the coordinating center (Independent Ethic Committee of the University of Cagliari, Number: MCF-SO-003 NP/2020/1770) and, thereafter, by all the participating centers.

RESULTS

Study population

All clinical records of patients with CD in an active follow-up at 20 IBD tertiary centers from January 2016 to December 2020 were retrospectively reviewed. Five hundred ninety-three patients with CD previously exposed to TNFi and treated with either UST or VDZ as second-line therapies were identified. One hundred twenty-three patients (20.7%) were excluded because of clinically inactive disease (an HBI <5) at baseline or incomplete data (Figure 1). Four hundred seventy patients, all Whites, met the inclusion criteria and were included in the analysis. Two hundred thirty-nine patients (50.9%) were treated with UST, whereas 231 patients (49.1%) received VDZ. Baseline patient characteristics were similar between the 2 groups, except for age (median 41 years [IQR 32.5–42] UST vs 47 years [IQR 37–59] VDZ; $P =$

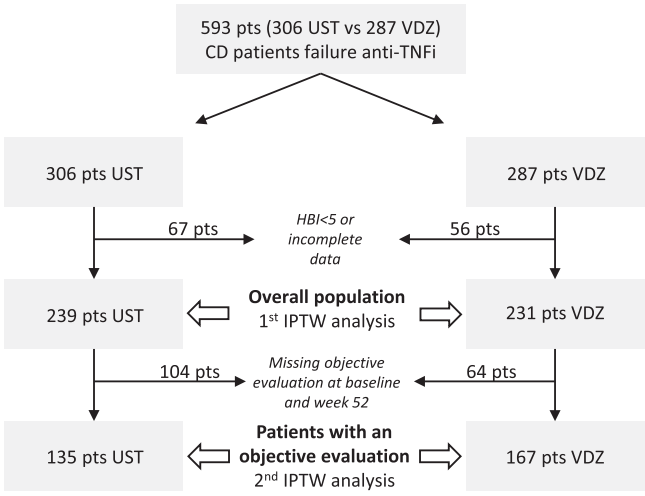

Figure 1. Patient disposition in the UST and VDZ treatment arms. HBI, Harvey-Bradshaw Index; IPTW, inverse probability of treatment weighting; TNFi, tumor necrosis factor-alpha inhibitor; UST, ustekinumab; VDZ, vedolizumab.

0.0004) and age at diagnosis (median 26 years [IQR 6–20] UST vs 32 years [IQR 7–17] VDZ; $P < 0.0001$), for extraintestinal manifestations (42.7% UST vs 10.3% VDZ; $P = 0.001$) and steroid use (31.4% UST vs 49.4% VDZ; $P < 0.0001$; Table 1) at baseline. Other baseline characteristics, including disease activity at baseline, disease phenotype (behaviour and location), number of previous TNFi, reason for TNFi discontinuation, disease duration, and concomitant immunosuppressive therapy, were balanced. After propensity score weighting, no difference between the 2 groups was observed, and the standardized difference was less than 0.1 for all variables included (Figure 2a).

Effectiveness: overall population analysis

At week 26, in the weighted overall population, clinical response rates were similar between the 2 groups (UST 60.1% vs VDZ 65.4%, $P = 0.277$), and no statistically significant differences were observed for clinical remission (UST 42.1% vs VDZ 44.8%) and SFR (UST 38.3% vs VDZ 40.7%; Table 2 and Figure 2b).

At week 52, clinical response rates were again similar between the groups (UST 64.6% vs VDZ 68.4%). However, clinical remission (UST 42.5% vs VDZ 55.5%, OR 1.69, 95% CI 1.13–2.52, $P = 0.010$) and SFR (UST 40.6% vs 51.1 VDZ %, OR 1.53, 95% CI 1.02–2.28, $P = 0.038$) rates were higher in the VDZ-treated patients (Table 2 and Figure 2c). The same results were replicated after application of propensity score matching (see Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/C489 and Supplementary Figures 1, Supplementary Digital Content 2, http://links.lww.com/AJG/C490 and 2, Supplementary Digital Content 3, http://links.lww.com/AJG/C491) and non-responder imputation of missing data at week 52 as sensitivity analysis (see Supplementary Figure 3, Supplementary Digital Content 4, http://links.lww.com/AJG/C492). No difference in dose escalation was observed between the UST and VDZ groups at week 26 (16.3% vs 17.7%) and week 52 (22.4% vs 22.2%).

As for biomarker evaluation, CRP and FC were available in 87.2% and 78.1% and in 36.2% and 39.1% of patients at weeks 26 and 52, respectively. CRP normalization rate in the weighted population was similar between the UST and VDZ groups at week 26 (UST 50.0% vs VDZ 54.0%) and week 52 (UST 56.3% vs VDZ 61.5%, Figure 2d). The mean FC value was 741 ± 160 mg/kg (mean ± SE) and 516 ± 83 mg/kg in the UST and VDZ groups, respectively, at baseline (P = ns). FC decreased at weeks 26 and 52 in both groups (week 26 UST 294 ± 46 vs VDZ 296 ± 59 and week 52 UST 204 ± 38 vs VDZ 261 ± 73) and did not differ between treatments (Figure 2e).

Effectiveness of UST and VDZ in patients with an objective evaluation

Among 470 patients with CD included in the study, 302 patients (135 UST [44.7%] and 167 VDZ [55.3%]), had an objective evaluation. Patients were included in the objective response evaluation if results from the same technique were available both at baseline and at week 52. Two hundred forty-nine patients (82.5%) had endoscopy, 168 (55.6%) small bowel ultrasound, and 105 (31.2%) CT/MR enteroclysis at baseline and week 52. Seventy-five patients (24.8%) were evaluated by all 3 diagnostic methods, while disease activity was assessed by 2 objective methods in 70 (23.2%). The remaining 157 patients (52.0%) were evaluated by a single technique. The grade of agreement among techniques was moderate to substantial (agreement analysis is available as Supplementary Material, Supplementary Digital Content 1, http://links.lww.com/AJG/C489).

Propensity score was recalculated based on the clinical characteristics of patients with an objective evaluation of disease activity (see Supplementary Table 2, Supplementary Digital Content 1, http://links.lww.com/AJG/C489 and Figure 3a), and the clinical outcomes from this subset of patients were consistent with those observed in the overall population (see Supplementary Figure 4, Supplementary Digital Content 5, http://links.lww.com/AJG/C493). In particular, more patients with an objective evaluation treated with VDZ were in clinical remission at week 52 when compared with those treated with UST (UST 42.1% vs VDZ 55.9%, OR 1.76, 95% CI 1.04–2.99, $P = 0.037$). However, objective response and remission rates were not different between the groups (objective response UST 72.4% vs VDZ 62.6%; objective remission UST 29.9 vs VDZ 28.5, Figure 3b). The composite outcomes clinical remission with objective response or remission was also not statistically different (clinical remission with objective response UST 37.2% vs VDZ 44.5%; clinical remission with objective remission UST 16.0% vs VDZ 22.5%). Results were replicated by applying PMS (see Supplementary Table 3, Supplementary Digital Content 1, http://links.lww.com/AJG/C489 and Supplementary Figures 5, Supplementary Digital Content 6, http://links.lww.com/AJG/C494, and 6, Supplementary Digital Content 7, http://links.lww.com/AJG/C495).

Predictive factors of steroid-free remission at week 52

In a univariate analysis, the baseline parameters, previous failure to both infliximab and adalimumab, use of immunomodulators and steroids at baseline, a history of surgery, and moderate-to-severe disease activity, were negatively associated with UST-induced steroid-free remission at week 52. After a multivariate logistic regression analysis considering variables with $P < 0.1$ at the univariate analysis, only the following baseline parameters remained negatively associated with SFR at week 52: use of immunomodulators (OR 0.24, 95% CI 0.41–1.29, $P = 0.03$) and steroids (OR 0.40, 95% CI 0.22–0.76, $P = 0.005$), moderate-to-severe disease activity (OR 0.48, 95% CI 0.27–0.85, $P = 0.011$), and previous CD-related surgery (OR 0.44, 95% CI 0.24–0.79, $P = 0.007$) (see Supplementary Table 4, Supplementary Digital Content 1, http://links.lww.com/AJG/C489). Regarding baseline variables of VDZ-treated

Table 1. Baseline Crohn's disease overall population characteristics before inverse propensity score of treatment weighting

	UST (n = 239)	VDZ (n = 231)	*P*
Age	41 (32.5–42)	47 (37–59)	0.0004[a]
Age at diagnosis	26 (19–35)	32 (23–44.75)	<0.0001[a]
HBI at baseline	8 (7–10)	8 (7–10)	0.053
Disease duration	12 (6–20)	11 (7–17)	0.882
Sex(male)	129 (54.0)	122 (26.1)	0.801
Appendectomy	77 (32.2)	53 (22.9)	0.046
Active smokers	152 (64.4)	149 (64.5)	0.205
Family history	24 (10.1)	20 (8.7)	0.607
Extraintestinal manifestations	102 (42.7)	66 (10.3)	0.001
Disease behavior			0.141
B1	80 (33.5)	85 (37.0)	
B2	107 (44.8)	112 (48.7)	
B3	52 (21.8)	34 (14.8)	
Disease location			0.099
L1	95 (39.7)	75 (32.6)	
L2	24 (10.0)	36 (15.7)	
L3	120 (50.2)	120 (52.2)	
Upper GI location (L4)	15 (6.3)	17 (7.4)	0.641
History of perianal disease	21 (8.8)	21 (9.1)	0.908
Previous anti-TNFi			0.752
Infliximab	44 (18.4)	48 (20.8)	
Adalimumab	92 (38.5)	90 (39.0)	
Both	103 (43.1)	93 (40.3)	
Reason for anti-TNFi discontinuation			0.565
Primary failure	22 (9.2)	23 (10.0)	
Secondary failure	164 (68.6)	148 (64.1)	
Intolerance	53 (22.2)	60 (26.0)	
Previous bowel resection	90 (37.7)	75 (32.5)	0.293
Steroids at baseline	75 (31.4)	114 (49.4)	<0.0001[a]
Immunomodulators at baseline	23 (9.6)	22 (9.5)	0.971

Data are presented as median (IQR) or n (%).
GI, gastrointestinal; HBI, Harvey-Bradshaw Index; IPTW, inverse probability of treatment weighting; IQR, interquartile range; TNFi, tumor necrosis factor-alpha inhibitor; UST, ustekinumab; VDZ, vedolizumab.
[a]*P* indicates statistical significance.

patients, previous exposure to adalimumab, steroids use at baseline, and moderate-to-severe disease activity were inversely associated with SFR at week 52. After the multivariate analysis, only baseline disease activity (OR 0.6, 95% CI 0.33–0.98, $P < 0.041$) maintained statistical significance. Clinical response at week 26 predicted SFR at week 52 in both UST-treated (OR 8.79, 95% CI 4.65–16.59, $P < 0.0001$) and VDZ-treated patients (OR 5.7, 95% CI 3.08–10.68, $P < 0.0001$; see Supplementary Table 5, Supplementary Digital Content 1, http://links.lww.com/AJG/C489).

After propensity score weighting, comparative efficacy between UST and VDZ in inducing SFR at week 52 was analyzed in different subgroups. VDZ was more effective than UST in patients who were younger than 40 years at diagnosis (OR 1.75, 95% CI 1.11–2.77, $P = 0.016$), without proximal gastrointestinal location (OR 1.56, 95% CI 1.03–2.36, $P = 0.036$), concomitantly treated with immunomodulators (OR 9.89, 95% CI 2.10–46.6, $P = 0.004$) or steroids at baseline (OR 2.33, 95% CI 1.18–4.62, $P = 0.015$), previously failing both adalimumab and infliximab (OR 2.55, 95% CI 1.34–4.85, $P = 0.004$), with mild-to-severe disease activity at baseline (OR 1.53, 95% CI 1.02–2.28, $P = 0.038$), and a history of perianal disease (OR 4.21, 95% CI 1.10–16.09 $P = 0.035$, see Supplementary Figure 7, Supplementary Digital Content 8, http://links.lww.com/AJG/C496).

Safety

AEs were recorded in 35 patients (14.6%) in the UST group and 39 patients (16.3%) in the VDZ group, most of which related to disease activity (17 [7.1%] UST and 24 [10.4%] VDZ). Excluding disease worsening, AEs were reported in 14 patients (5.9%) in the UST group and 15 patients (6.2%) in the VDZ group. The list of AEs is reported in Supplementary Material (see Supplementary Table 6, Supplementary Digital Content 1, http://links.lww.com/AJG/C489). The most common AEs were nasopharyngitis (5 patients in the VDZ group), arthralgia (4 patients, 2 in the UST and 2 in the VDZ group) and pneumonia (4 patients, 2 in the UST and 2 in the VDZ groups). Two patients in the VDZ group had more than 1 AE (cellulitis and eczema, cholestasis and hyperamylasemia).

Two serious AEs, requiring hospitalization, were recorded. One patient in the UST group developed abdominal abscesses. The event resolved after radiologic drainage of the abscess and antibiotic therapy. One case of sepsis occurred in a patient treated with VDZ related to central venous catheter infection. Sepsis was readily controlled after IV antibiotic therapy. No death was recorded in both groups of treatment.

DISCUSSION

UST and VDZ are frequently used as second-line therapies in patients with CD after TNF inhibitors, but prospective data comparing their efficacy are still missing. In the attempt to address this issue, retrospective comparative real-world studies in cohorts of patients in which TNFi failed have been performed. In a propensity score–weighted cohort of 237 patients with CD (107 treated with UST; 132 treated with VDZ), no difference in clinical remission was observed between the 2 groups. By contrast, at week 52, clinical remission but not SFR was significantly higher in UST-treated patients when compared with that in VDZ-treated patients (10). Data from a prospective Dutch registry, including 128 VDZ-treated and 85 UST-treated patients with CD showed, after propensity score matching and in line with our data, no difference in SFR at week 24, but at week 52, it was significantly higher in the UST group ($P = 0.004$) (11). Another retrospective study from UK considering 85 VDZ-treated and 45 UST-treated patients, SFR was higher in the UST group at 6 and 12 months (14). However, in this study, no propensity score was applied, and baseline characteristics of the 2 populations were unbalanced for number of previous TNF inhibitors use and reasons for discontinuation. Manlay et al. (13) published a retrospective study comparing a propensity score–weighted cohort of 224 UST-treated and 88 VDZ-treated patients. No differences were reported at week 24, whereas at week 52, a small but significant difference (Δ 10%) was

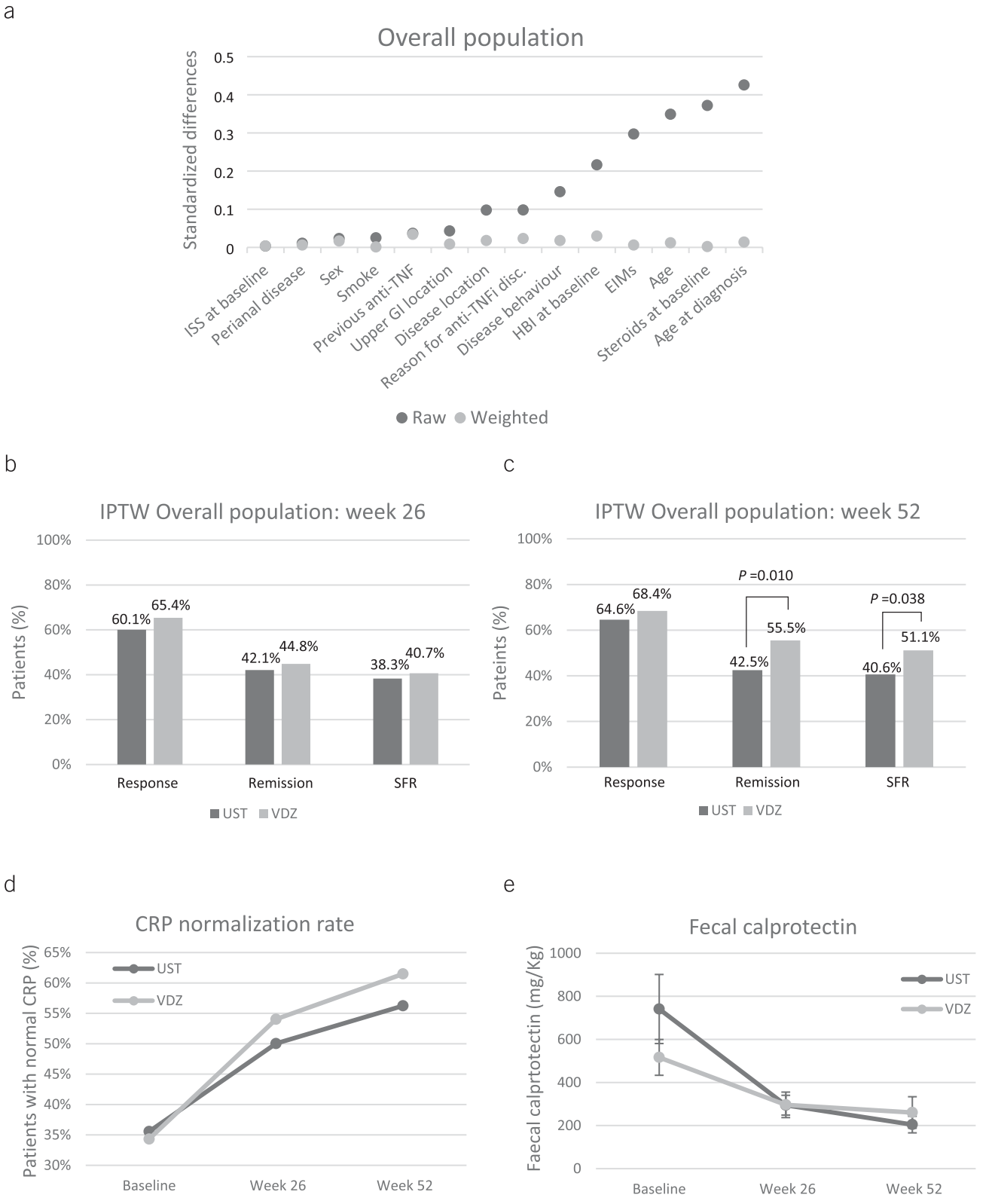

Figure 2. Standardized differences of relevant variables among UST-treated and VDZ-treated overall population before (raw) and after (weighted) application of the IPTW (**a**). Weighted clinical response, remission and SFR at week 26 (**b**) and week 52 (LOCF) (**c**). CRP normalization rate (**d**) and fecal calprotectin absolute values (mg/kg) (**e**) at baseline, week 26, and week 52 in UST-treated and VDZ-treated patients. *P* value indicates statistical significance. CRP, C-reactive protein; EIM, extraintestinal manifestation; GI, gastrointestinal; HBI, Harvey-Bradshaw Index; IPTW, inverse probability of treatment weighting; LOCF, last-observation carried forward; SFR, steroid-free remission; TNFi, tumor necrosis factor-alpha inhibitor; UST, ustekinumab; VDZ, vedolizumab.

Table 2. OR and 95% CI of clinical outcomes at W26 and W52

IPTW	OR (VDZ vs UST)	95% CI	*P*
W26 response	1.26	0.83–1.90	0.277
W26 remission	1.12	0.74–1.67	0.596
W26 SF remission	1.10	0.73–1.67	0.636
W52 response	1.19	0.78–1.81	0.426
W52 remission	1.69	1.13–2.52	0.010[a]
W52 SF remission	1.53	1.02–2.28	0.038[a]

CI, confidence interval; IPTW, inverse propensity of treatment weight; OR, odds ratio; UST, ustekinumab; VDZ, vedolizumab; W26, week 26; W52, week 52.
[a]*P* indicates statistical significance.

found in favor of UST. A recent meta-analysis including the aforementioned studies favored UST over VDZ in the induction of SFR at week 52 but not at week 14 (15).

Inversely, in a recent retrospective cohort considering 275 patients treated with UST, propensity score matched with an independent cohort of 118 patients treated with VDZ, clinical remission was higher among UST-treated patients at week 14 when compared with patients treated with VDZ. However, neither clinical remission nor therapy failure rates were significantly different after 1 year of therapy (12).

These contradicting results might result from the small sample size characterizing most of the aforementioned studies in addition to the absence of objective parameters to evaluate therapy effectiveness. In the attempt to tackle these limitations, we compared UST and VDZ in a large retrospective multicenter cohort including 470 patients with CD in which 1 or more TNFi failed. In our cohort, an objective evaluation by endoscopy, CT/MR-enteroclysis, and small bowel US were available in approximately two-thirds of the patients, and half of them was evaluated by 2 or more methodologies.

Results from our study showed no difference in clinical response, remission, and steroid-free remission after 6 months of treatment. After a year, in contrast with previously published data, patients treated with VDZ had higher clinical remission (OR 1.69, $P = 0.010$) and steroid-free remission (OR 1.53, $P = 0.038$) rates. However, UST and VDZ resulted equally effective in inducing objective response and remission at this time point.

In the attempt to interpret our results, we compared UST and VDZ response rates with those reported in the aforementioned studies. Remission and response to UST were in line with those previously reported, whereas VDZ rates were higher. A possible explanation is the lower number of previous TNFi and the concomitant use of immunosuppressants (ISS) at baseline in our study population when compared with the others, reflecting a population with less refractory disease and potentially better response to VDZ. Accordingly, data from retrospective cohorts of patients treated with VDZ and baseline characteristics more similar to ours showed similar efficacy results (20,21).

As for the objective evaluation, endoscopy was available in almost all patients (82.5%) and small bowel ultrasound and CT/MR enteroclysis in half and one-third, respectively. Disease activity was evaluated with more than 1 method in half of the patients. After 52 weeks of treatment, UST and VDZ resulted equally effective in inducing objective remission and response after propensity score weighting and matching application. Although available in a

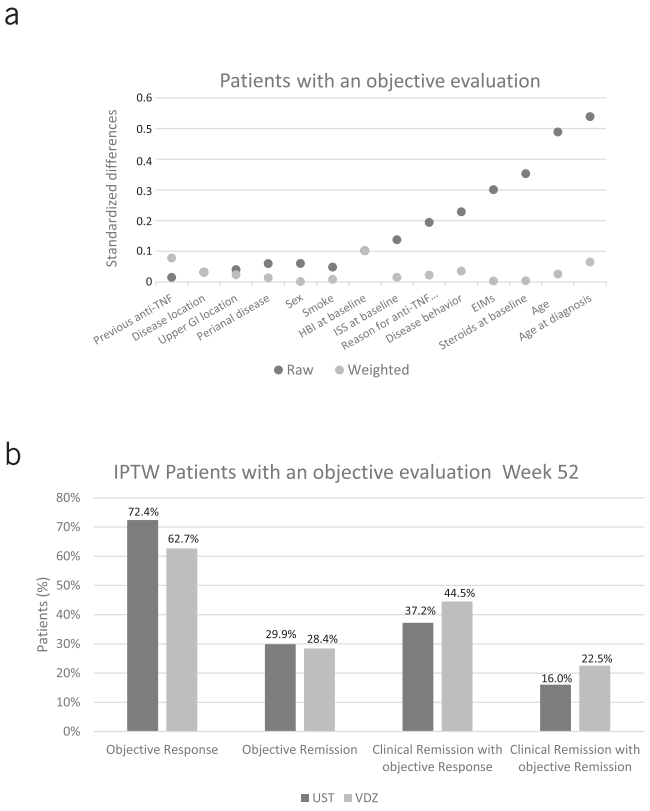

Figure 3. Standardized differences of relevant variables among UST-treated and VDZ-treated patients with an objective evaluation after 1 year of treatment before (raw) and after (weighted) application of the IPTW (**a**). Weighted objective response, remission and clinical remission with objective response and remission at week 52 in UST-treated and VDZ-treated patients (**b**). GI, gastrointestinal; HBI, Harvey-Bradshaw Index; IPTW, inverse probability of treatment weighting; TNF, tumor necrosis factor; UST, ustekinumab; VDZ, vedolizumab.

limited number of patients, the biomarkers CRP and FC also were not different between the 2 groups at the end of the observation period. These results suggest that in clinical practice, VDZ might be more effective than UST in inducing clinical but not endoscopic/transmural remission after 1 year of treatment. A delayed organ healing in VDZ-treated patients when compared with UST-treated patients well fits with the evidence of a delayed recruitment of cells involved in the repair process caused by VDZ (22).

In line with other studies, ISS at baseline did not improve remission rate, moderate-to-severe disease activity was associated with lower UST, and VDZ-induced SFR and clinical response at week 26 was predictive of SFR at week 52 in both UST-treated and VDZ-treated patients (11,13,19,23).

Patients treated with VDZ were more likely to reach SFR at week 52 if young at diagnosis (<40 years), with no proximal gastrointestinal lesions, ISS or steroids at baseline, failure to both TNFi, mild to severe disease activity at baseline, and a history of perianal disease. The positive association with the concomitant use of steroids and ISS and the absence of proximal gastrointestinal lesions are in line with previously published data (10,13). By contrast, we found a positive association between VDZ-induced SFR and a history of perianal disease. This result should be interpreted with caution though due to the exiguous number of patients with active perianal disease in both the treatment groups.

No specific safety signals were observed in our cohort of patients during the analyzed period. The rate of AEs reported in our cohort was relatively low. However, due to the retrospective nature of the study, it might be that most of the minor AEs did not deserve medical intervention and therefore were not reported in the medical records or some of them might have been managed by general practitioner (GP) and not reported during follow-up visits.

In addition to the retrospective design and the relatively short period of observation, the absence of validated score systems to quantify endoscopic and transmural changes represents a limit of the study. However, we used objective parameters commonly reported in clinical records to describe therapy-induced objective effects as previously reported in other similar retrospective cohorts (18,19).

Objective outcomes were evaluated with the same technique in a subgroup of patients representing roughly two-thirds of the overall population. Baseline patient characteristics and the independent application of the propensity score methodology to this subpopulation minimized possible difference between the groups of treatment. Accordingly, clinical outcomes in patients with objective evaluation were consistent with those observed in the overall population. However, the application of this out of standard-of-care approach consisting in the evaluation of objective outcomes with 1 or more technique might have been induced by the presence of more aggressive and refractory disease, thus introducing a potential selection bias that cannot be completely excluded.

Despite the robust application of propensity score in our study that considers the effect of relevant variable known to affect outcomes, we acknowledge, as a limitation of this methodology, that other variables not included in the model might still have a residual confounding effect.

In conclusion, UST and VDZ showed similar effectiveness in reaching clinical outcomes after 6 months of treatment in patients in which TNFi previously failed. At 1 year, althoughVDZ was more effective than UST in inducing clinical remission, objective response and remission were similar between treatments. In light of the current literature and of the data reported here, pragmatic prospective trials are needed to better define in a real-world setting the position of UST and VDZ as second-line therapies in patients with CD in which TNFi failed.

CONFLICTS OF INTEREST

Guarantor of the article: Massimo C. Fantini, MD, PhD.

Specific author contributions: S.O. and M.C.F.: conception and design of the study. D.P., L.B., O.M.N., G.F., C.M., A.V., M.B.P., C.B., A.A., S.C., D.G.R., S.M., F.M., G.B., G.M., A.M., L.S., and S.S.: data generation, collection, and assembly. A.F., L.M., S.O., and M.C.F.: analysis and interpretation of the data. S.O., F.A.C., A.A., and M.C.F.: drafting and critical revision of the manuscript. S.O., F.A.C., A.A., W.F., A.O., and M.C.F.: approval of the final version of the manuscript.

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Study Highlights

WHAT IS KNOWN

- ✓ Randomized controlled trials have demonstrated the efficacy of both ustekinumab and vedolizumab, 2 biologics with different mode of action, in inducing clinical and endoscopic remission in Crohn's disease refractory to conventional and anti-TNF therapies. However, prospective head-to-head trials comparing ustekinumab and vedolizumab in this clinical setting are currently missing. A recent meta-analysis including real-world studies showed no difference between the 2 treatments in steroid-free clinical remission at the end of induction, while ustekinumab proved to be superior at 1 year of therapy. However, in all the study included in the meta-analysis, an objective evaluation of disease activity was missing.

WHAT IS NEW HERE

- ✓ In a large multicenter retrospective cohort of Crohn's disease in which anti-TNF therapy failed, vedolizumab and ustekinumab were equally effective in inducing clinical response after 6 months of therapy.
- ✓ After 1 year, a small but significant superiority of vedolizumab over ustekinumab in inducing clinical remission was observed. However, this was not paralleled by difference in objective outcomes including biomarkers, endoscopy, and cross-sectional imaging such as magnetic resonance/computed tomography enteroclysis or small bowel ultrasound.
- ✓ The composite outcomes clinical remission with objective remission or response showed no difference between ustekinumab-treated and vedolizumab-treated patients after 1 year of therapy.

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