Comparative Efficacy of Vedolizumab and Ustekinumab as First-Line Biologic Therapies in Biologic-Naive Patients with Moderate-to-Severe Active Crohn's Disease: Postprint

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Abstract

Background Vedolizumab (VDZ) and ustekinumab (UST) are both effective for the treatment of Crohn's disease (CD). However, there are limited comparative studies of the two agents as first-line biologic therapy in CD patients.

Objective To compare the efficacy and safety of VDZ and UST as first-line biologic agents in patients with moderate-to-severe active CD in a real-world setting, and to identify predictors associated with clinical efficacy.

Methods Data were retrospectively collected from patients with moderate-to-severe CD who received VDZ or UST as first-line biologic therapy at the First Affiliated Hospital of Zhejiang Chinese Medical University between January 2021 and January 2023. Clinical efficacy at 14 and 52 weeks of treatment, endoscopic efficacy at 52 weeks, and drug maintenance therapy rates were evaluated. Factors influencing clinical remission at 52 weeks were analyzed, and adverse drug reactions during treatment were recorded.

Results A total of 72 CD patients were enrolled, including 27 in the VDZ group and 45 in the UST group; 67 patients completed 14 weeks of treatment (24 VDZ, 43 UST), and 57 patients completed 52 weeks of treatment (18 VDZ, 39 UST). There were no statistically significant differences in clinical response rates or clinical remission rates between UST and VDZ at 14 weeks ($P>0.05$). There were no statistically significant differences in clinical response rates or clinical remission rates between UST and VDZ at 52 weeks ($P>0.05$). There were no statistically significant differences in endoscopic response rates or endoscopic remission rates between UST and VDZ at 52 weeks ($P>0.05$). The 52-week drug maintenance therapy rate was higher for UST [86.7% (39/45)] than for VDZ [66.7% (18/27)] ($P=0.043$). Multivariate logistic regression analysis showed that age (OR=0.965, 95%CI=0.938~0.993) and clinical response at

14 weeks (OR=8.483, 95%CI=1.699~42.352) were influencing factors for clinical remission at 52 weeks in UST patients (P<0.05). Since no factors influencing clinical remission at 52 weeks were identified for VDZ in the univariate analysis, no multivariate analysis was performed. There was no statistically significant difference in the incidence of adverse events between VDZ [7.4% (2/27)] and UST [4.4% (2/45)] (P>0.05).

Conclusion As a first-line biologic agent, UST demonstrates comparable clinical and endoscopic efficacy to VDZ in patients with moderate-to-severe active CD, but the 52-week drug maintenance therapy rate of UST is higher than that of VDZ. Age and clinical response to UST at 14 weeks are associated with clinical remission at 52 weeks of UST treatment. The incidence of adverse reactions is similar between the two agents.

Full Text

Comparison of the Efficacy of Vedolizumab and Ustekinumab as First-Line Biologic Therapies in Patients with Moderately to Severely Active Crohn's Disease

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Abstract

Background: Vedolizumab (VDZ) and ustekinumab (UST) are both effective treatments for Crohn's disease (CD). However, there are fewer comparative studies of these biologics as first-line therapy in biologic-naïve patients with CD.

Objective: To compare the efficacy and safety of real-world UST and VDZ as first-line biologic therapies in biologic-naïve patients with moderately to severely active CD, and to identify predictive factors associated with clinical efficacy.

Methods: We retrospectively collected data from patients with moderately to severely active CD who received VDZ or UST as their first biologic agent at the First Affiliated Hospital of Zhejiang Chinese Medical University between January 2021 and January 2023. Clinical efficacy at Weeks 14 and 52, endoscopic efficacy at Week 52, and treatment persistence were evaluated. Factors influencing clinical remission at Week 52 were analyzed, and adverse drug reactions were documented.

Results: A total of 72 patients with CD were included (27 receiving VDZ and 45 receiving UST). Sixty-seven patients completed 14 weeks of treatment (24

VDZ and 43 UST), and 57 completed 52 weeks of treatment (18 VDZ and 39 UST). There were no statistically significant differences in clinical response rates or clinical remission rates at 14 weeks between UST and VDZ (P>0.05). Similarly, at 52 weeks, no statistically significant differences were observed in clinical response rates, clinical remission rates, endoscopic response rates, or endoscopic remission rates between the two treatments (P>0.05). However, UST demonstrated a higher 52-week treatment persistence rate [86.7% (39/45)] compared to VDZ [66.7% (18/27)] (P=0.043). Multifactorial logistic regression analysis indicated that age (OR=0.965, 95%CI=0.938-0.993) and clinical response at Week 14 (OR=8.483, 95%CI=1.699-42.352) were significant predictors of clinical remission at Week 52 in UST-treated patients (P<0.05). No multifactorial analysis was conducted for VDZ as no factors influencing clinical remission at Week 52 were identified in the univariate analysis. Adverse event rates were 7.4% (2/27) for VDZ and 4.4% (2/45) for UST, with no statistically significant difference between the groups (P>0.05).

Conclusion: The clinical and endoscopic efficacy of UST as a first-line biologic therapy in biologic-naïve patients with moderately to severely active CD is comparable to VDZ. However, UST demonstrated a higher 52-week treatment persistence rate. Age and clinical response at Week 14 correlate with clinical remission at Week 52 in UST-treated CD patients. The safety profiles of both agents were similar.

Key words: Crohn's disease; Vedolizumab; Ustekinumab; Biologics; Comparative effectiveness research

Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disorder characterized by persistent abdominal pain, diarrhea, weight loss, and fatigue. As the disease progresses, some patients develop complications such as abscesses, strictures, and perforations, leading to irreversible intestinal damage that severely impacts health and quality of life [1]. Biologic therapy has been proven to induce remission in CD and reduce hospitalization and colectomy rates [2]. Ustekinumab (UST) and vedolizumab (VDZ) were approved in China in March and November 2020, respectively. Given their distinct mechanisms of action, efficacy profiles, and safety characteristics, selecting between these agents remains a clinical challenge. Since real-world clinical data on VDZ and UST for CD patients in China are limited, this single-center retrospective cohort study aimed to compare the safety and efficacy of VDZ and UST as first-line biologic therapies in patients with moderately to severely active CD, providing evidence to guide clinical decision-making.

Methods

Study Population

We retrospectively collected data from patients with moderately to severely active CD who received VDZ or UST as their first biologic agent at the First Affiliated Hospital of Zhejiang Chinese Medical University between January 2021 and January 2023. The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University (2024-KL-358-01).

Inclusion Criteria

1. Diagnosis of CD according to the Consensus on Diagnosis and Treatment of Inflammatory Bowel Disease (2018 • Beijing) [3];
2. Crohn's Disease Activity Index (CDAI) [4] >220;
3. VDZ or UST as first-line biologic therapy;
4. Age between 16 and 80 years.

Exclusion Criteria

1. Contraindications to VDZ or UST: allergy to any component or active infection;
2. Prior biologic therapy;
3. Malignancy;
4. Severely incomplete medical records.

Study Methods

Data Collection Baseline characteristics were recorded, including age, sex, disease duration, Montreal classification [5] (age at diagnosis, disease location, disease behavior), perianal disease, intestinal surgery history, and CD-related medication use. Endoscopic findings were also documented.

Treatment Protocols The UST induction regimen was weight-based: 260 mg for patients $ $55 kg, 390 mg for 55-85 kg, and 520 mg for >85 kg, all administered intravenously. Maintenance therapy consisted of 90 mg subcutaneous injections every 8 or 12 weeks. The VDZ regimen involved intravenous infusions of 300 mg at Weeks 0, 2, and 6 during induction, followed by maintenance doses every 8 weeks.

Efficacy and Safety Assessment CDAI scores were recorded at baseline and at Weeks 14 and 52. The CDAI comprises multiple components including stool frequency, abdominal pain severity, abdominal mass, and body weight. Scores of 150-220 indicate mild activity, >220-450 moderate activity, and >450 severe activity. Clinical remission was defined as CDAI <150, and clinical response as a decrease from baseline of

$ 70points[6].Endoscopicevaluationswereperformedwithin4weeksbeforetreatmentinitiationandat Week52(± weeks), assessed using the Simple Endoscopic Score for Crohn's Disease (SES-CD) [7]. The SES-CD scores ulcer size, ulcerated surface area, extent of bowel involvement, and presence of strictures on a 0-3 scale, with higher scores indicating more severe disease. Endoscopic response was defined as $ $50% reduction in SES-CD from baseline, and endoscopic remission as total SES-CD $ $2. Adverse events were collected from clinical records during treatment.

Statistical Analysis

Data were analyzed using SPSS 25.0 software. Continuous variables were expressed as median (P25, P75) and compared between groups using the Wilcoxon rank-sum test. Categorical variables were expressed as percentages and compared using the chi-square test. Multifactorial logistic regression analysis was used to explore factors influencing clinical remission at Week 52. P<0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 72 patients with CD were included (27 VDZ, 45 UST). Three VDZ-treated patients and two UST-treated patients switched therapies before Week 14 due to inadequate response, leaving 67 patients who completed 14 weeks of treatment (24 VDZ, 43 UST). Baseline comparisons revealed significant differences in age and age at diagnosis between VDZ and UST groups (P<0.05) .

When evaluating 52-week efficacy, nine patients (5 VDZ, 4 UST) discontinued due to inadequate response and switched therapies, and one VDZ-treated patient withdrew due to interstitial pneumonia. Ultimately, 57 patients completed 52 weeks of treatment (18 VDZ, 39 UST). Significant differences in age and age at diagnosis persisted between groups at Week 52 (P<0.05) .

Efficacy Comparison

At Week 14, UST achieved clinical response in 76.7% (33/43) and clinical remission in 37.2% (16/43) of patients, compared to 70.8% (17/24) and 33.3% (8/24) for VDZ, respectively. No statistically significant differences were observed in clinical response or remission rates between UST and VDZ at Week 14 (^{2}=0.284, P=0.594; ^{2}=0.101, P=0.751).

At Week 52, UST demonstrated clinical response in 89.7% (35/39) and clinical remission in 59.0% (23/39) of patients, versus 83.3% (15/18) and 55.6% (10/18) for VDZ, respectively. Again, no statistically significant differences were found in clinical response or remission rates between the two treatments (^{2}=0.063, P=0.802; ^{2}=0.059, P=0.808).

For endoscopic outcomes at Week 52, seven patients (2 VDZ, 5 UST) did not undergo endoscopy due to personal reasons, leaving 16 VDZ and 34 UST patients for evaluation. UST achieved endoscopic response in 88.2% (30/34) and endoscopic remission in 52.9% (18/34) of patients, compared to 81.3% (13/16) and 43.8% (7/16) for VDZ, respectively. No statistically significant differences were observed in endoscopic response or remission rates between UST and VDZ (^{2}=0.052, P=0.820; ^{2}=0.368, P=0.544).

52-Week Drug Maintenance Rate

The 52-week treatment persistence rate was significantly higher for UST [86.7% (39/45)] compared to VDZ [66.7% (18/27)] (^{2}=4.093, P=0.043).

Factors Influencing Clinical Remission at Week 52

Univariate analysis of patients who completed 52 weeks of treatment identified age (P=0.001), perianal disease (P=0.037), and clinical response at Week 14 (P=0.004) as factors associated with clinical remission at Week 52 in the UST group . Variables with P<0.05 in univariate analysis were entered into multivariate logistic regression analysis, with clinical remission at Week 52 as the dependent variable (0=not in remission, 1=in remission) and age (continuous variable), perianal disease (0=absent, 1=present), and clinical response at Week 14 (0=no, 1=yes) as independent variables. Multivariate analysis revealed that age (OR=0.965, 95%CI=0.938-0.993) and clinical response at Week 14 (OR=8.483, 95%CI=1.699-42.352) were significant predictors of clinical remission at Week 52 in UST-treated patients (P<0.05) . No multivariate analysis was performed for VDZ as no factors influencing Week 52 clinical remission were identified in the univariate analysis.

Adverse Events

Adverse event rates were low for both treatments. VDZ was associated with adverse events in 7.4% (2/27) of patients, including one case of interstitial pneumonia with infection and one case of pruritus. UST had adverse events in 4.4% (2/45) of patients. There was no statistically significant difference in adverse event rates between VDZ and UST (^{2}=0.282, P=0.595). The VDZ patient with interstitial pneumonia discontinued therapy due to the adverse event, while the VDZ patient with pruritus and both UST patients with adverse events continued their original biologic therapy after symptomatic management.

Discussion

The incidence of CD has been increasing annually in recent years [8]. UST and VDZ are commonly used as second-line therapies after tumor necrosis factor-alpha (TNF-α) inhibitor failure, but data on their efficacy as first-line biologic agents remain limited. This retrospective cohort study addresses this gap by focusing on biologic-naïve patients.

In terms of drug efficacy, 67 and 57 patients completed 14-week and 52-week treatment periods, respectively. Our study found that UST demonstrated comparable early and long-term efficacy to VDZ. An Italian retrospective study of 470 CD patients reported superior 52-week clinical efficacy for VDZ compared to UST [9]. Other studies have suggested UST is more effective than VDZ at 8 and 52 weeks [10]. Conversely, Lenti et al. [11] found UST more effective at 14 weeks but not significantly different at 52 weeks. These conflicting results may be attributed to variations in sample size, baseline characteristics, and whether propensity score matching was employed. Several factors may explain our findings: unlike other studies where patients had failed at least one biologic therapy and represented a more refractory population, our cohort was biologic-naïve. Additionally, baseline differences existed between VDZ and UST groups in age and age at diagnosis. While some studies suggest age or age at diagnosis does not affect UST efficacy [12] and Lenti et al. [13] found no correlation between these factors and VDZ efficacy, other research indicates younger age is associated with better clinical outcomes with infliximab [14], while older age at diagnosis may predict better drug response and prognosis [15]. However, some studies have found no association between age or age at diagnosis and biologic efficacy [16-17].

Our study also examined 52-week drug maintenance rates, finding higher persistence with UST than VDZ. A French multicenter study similarly reported lower primary non-response rates (6.7% vs. 14.8%, P=0.034) and reduced long-term risk of treatment discontinuation due to failure (HR=1.53, P=0.029) with UST compared to VDZ [18]. Interpretation of our results may also be influenced by the fact that 26.7% (12/45) of UST-treated patients underwent treatment optimization (re-induction with intravenous dosing, shortening injection intervals to 4-6 weeks, or both), compared to only 14.8% (4/27) of VDZ patients who had interval shortening. Fumery et al. [19] demonstrated that UST intensification could restore clinical response in two-thirds of patients. This may be related to drug concentrations, though not all studies support this association. A recent French single-center study of 42 refractory CD patients found no correlation between UST trough levels and clinical response [20], necessitating further investigation.

Knowledge of specific predictors for clinical remission remains limited. Interestingly, our study identified variables that may help predict Week 52 clinical remission with UST. After univariate analysis of baseline data including age, sex, disease location, disease duration, perianal disease, and gastrointestinal surgery history, variables with $P<0.05$ were entered into multivariate analysis. We found that younger age and clinical response at Week 14 were associated with higher likelihood of achieving Week 52 clinical remission. Predictive factors for clinical efficacy have been suggested in other studies as well. The UNITI trial [21] reported higher clinical response rates in female and Caucasian patients. A German study of 106 CD patients found that penetrating complications were associated with lower clinical and biochemical remission rates at Week 48 (OR=0.25, 95%CI=0.07-0.89) [22]. Other research has linked older age

with poorer UST response [23], and Feagan et al. [21] showed better short-term clinical efficacy at 6 weeks in younger patients (OR=2.4, 95%CI=1.3-4.3), consistent with our findings. Unfortunately, we did not identify predictors of Week 52 clinical remission for VDZ, likely due to the smaller sample size. Increasing attention is being directed toward identifying predictors of drug efficacy [24-25]. As a chronic inflammatory disease causing irreversible intestinal damage, CD affects a substantial proportion of patients requiring biologic therapy. While biologics are more effective than conventional drugs, some patients still fail to achieve adequate clinical or endoscopic response. Identifying factors associated with higher efficacy would enable personalized drug selection, maximizing therapeutic benefit while minimizing costs.

Adverse events with biologics remain a clinical priority. VDZ, a gut-selective humanized monoclonal antibody, primarily causes gastrointestinal events and infections, with few serious adverse reactions [26]. UST safety has also been well-established in numerous clinical studies [27-28]. Our study found low adverse event rates for both agents, though lower than reported in other studies, possibly due to our smaller sample size, the retrospective nature of the study (where minor adverse events without medical intervention may not have been documented), and the fact that our biologic-naïve population had less complex treatment histories than cohorts who had failed prior biologics. Overall, both VDZ and UST demonstrated favorable safety profiles as first-line biologic therapies.

The primary strengths of this study include the single-center retrospective design, which ensured data uniformity, high follow-up accuracy, and good patient compliance, providing a realistic reflection of treatment patterns in the Chinese population. Objective endoscopic assessment also enhanced accuracy. However, limitations exist: baseline differences in age and age at diagnosis between VDZ and UST groups were present without propensity score matching. While some real-world studies [11] recommend VDZ for elderly patients with comorbidities and UST for younger patients, our univariate analysis did not find these baseline differences affected clinical outcomes. Second, the retrospective design may have introduced unmeasured confounders. Finally, the single-center source and relatively small sample size may have introduced statistical bias. Large-scale, long-term efficacy and safety assessments are necessary for CD management.

In conclusion, as a first-line biologic therapy for moderately to severely active CD, UST demonstrates comparable clinical and endoscopic efficacy to VDZ, with better improvement in endoscopic findings and control of intestinal inflammation. Notably, UST showed significantly higher 52-week treatment persistence rates. Younger age and clinical response at Week 14 correlate with Week 52 clinical remission in UST-treated patients. Both agents exhibited similar safety profiles.

Author Contributions: Liu Liu contributed to study design, implementation, data collection, statistical analysis, data interpretation, and manuscript writing. Xu Wenhang was responsible for data collection, table preparation,

and statistical analysis. Lü Bin provided critical review and guidance on intellectual content. Fan Yihong oversaw quality control, took overall responsibility for the article, provided supervision and management, and secured funding.

Conflict of Interest: The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.