Vedolizumab Induces Endoscopic and Histologic Remission in Patients With Crohn's Disease

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BACKGROUND & AIMS: We evaluated the ability of vedolizumab to induce endoscopic and histologic remission in patients with Crohn's disease (CD). **METHODS:** We performed a prospective study of 110 patients with active CD, based on CD activity index (CDAI) scores >220 and mucosal ulcerations, who received open-label vedolizumab (300 mg) infusions at weeks 0, 2, and 6, and every 8 weeks thereafter through week 52 at tertiary centers in Europe. Patients received an additional infusion at week 10 if their CDAI score had not decreased by 70 points. Patients underwent ileocolonoscopy with collection of biopsies at baseline and weeks 26 and 52; a local and central reader determined simple endoscopic index for CD (SES-CD) scores. Histologic features were assessed by a blinded pathologist at week 26. Serum concentrations of vedolizumab were measured at serial time points. The primary outcome was endoscopic and histologic remission in patients with active CD treated with vedolizumab for 52 weeks. **RESULTS:** At weeks 26 and 52, 36 patients (29%) and 34 patients (31%), respectively, were in corticosteroid-free clinical remission (CDAI score <150), respectively. Based on intent-to-treat analysis, endoscopic remission (SES-CD score <4) was achieved by 36 patients (33%) and 40 patients (36%) at weeks 26 and 52. Endoscopic responses (decrease in SES-CD score ≥50%) occurred in 44 patients (40%) at week 26 and 5 patients (45%) at week 52. Serum concentrations of vedolizumab were higher at weeks 2, 10, and 22 in patients with lower SES-CD scores. Histologic remission at week 26 was observed in 43 (64%) of 67 patients based on Geboes Score and 37 (66%) of 56 patients based on Robarts Histopathology Index scores in analyses of paired biopsies with inflammation at baseline. Serum concentrations of vedolizumab above 10 mg/L at week 22 were associated with endoscopic remission at week 26. **CONCLUSIONS:** In a prospective trial, we found that approximately one-third of patients with CD achieve endoscopic remission after 52 weeks of treatment with vedolizumab and two-thirds achieve histologic remission at week 26. Higher serum concentrations of vedolizumab were associated with better outcomes. EUDRACT no: 2014–005376–29.

Crohn's disease (CD) is a chronic disabling disease that can affect the entire gastrointestinal tract.[1] Symptoms commonly include abdominal pain, diarrhea, weight loss, and fatigue. Vedolizumab (VDZ) is a gut-selective humanized monoclonal antibody that binds to the α4β7 integrin, thereby inhibiting leucocyte vascular adhesion and migration into the gastrointestinal mucosa. VDZ is approved for the treatment of moderate to severe CD, based on results of the GEMINI 2 and 3 phase 3 randomized controlled trials.[2,3] Although the efficacy and safety of VDZ induction and maintenance therapy in CD has been confirmed in real-life cohorts, only limited data are available on endoscopic and histological remission.[4–8]

Endoscopic remission is an important treatment goal in CD that is associated with improved clinical outcomes, including reduced hospitalization and surgery rates.[9,10] Moreover, endoscopic response is recommended as a co-primary endpoint in clinical trials by regulatory agencies.[11] Nonetheless, only a few studies have investigated endoscopic remission with VDZ in CD and these have reported on highly selected patients. Noman and colleagues[4] studied 29 patients with CD who participated in the open-label extension phase of the GEMINI 2 trial. Endoscopic

CLINICAL AT

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Although the efficacy and safety of vedolizumab induction and maintenance therapy of Crohn's disease (CD) has been confirmed, few data are available on endoscopic and histologic remission.

NEW FINDINGS

Vedolizumab treatment induces endoscopic and histologic remission in patients with CD. Higher serum concentrations of vedolizumab are associated with endoscopic remission. Serum concentrations of vedolizumab above 10 mg/L at week 22 were associated with endoscopic remission at week 26.

LIMITATIONS

This was an open-label study design. However, endoscopic and histologic outcomes were assessed blindly.

IMPACT

These findings can be used in prospective dose-optimization studies, to determine whether dose intensification of vedolizumab can further improve outcomes in patients with CD.

remission, defined as disappearance of ulcers seen at endoscopy, was observed in 29% of patients receiving VDZ. In the largest experience, Dulai et al[5] and the Victory consortium reported results from a cohort study of 212 patients with CD who received VDZ and showed a high 12-month cumulative endoscopic remission rate of 63% (defined as absence of ulcers and/or erosions) in a subset of patients. However in this study, endoscopy was performed according to clinical practice, in distinction to predefined intervals, and it was unclear how these patients were selected for inclusion in the analyses. Importantly, site investigators evaluated the endoscopies, in distinction to blinded central readers (CRs). This circumstance may have resulted in an overestimation of treatment efficacy.

In the past decade, multiple studies of tumor necrosis factor (TNF) antagonists have shown better clinical outcomes in patients with higher drug exposures.[12–14] Likewise, a positive association between VDZ serum concentrations and clinical remission was reported in a post hoc analysis of the GEMINI 2 and 3 trials.[15] However, exposure-efficacy relationships for endoscopic and histological outcomes, 2 objective measures of pharmacodynamic effects, have not been previously reported in VDZ-treated patients with CD.

The primary objective of the present study was to explore endoscopic and histological outcomes in patients with active CD treated with VDZ for 52 weeks. As a secondary objective, we evaluated pharmacokinetic/pharmacodynamic relationships for these endpoints (LOVE-CD: LOw countries VEdolizumab in CD; EUDRACT number: 2014-005376-29).

Materials and Methods

In LOVE-CD, adult patients with CD (≥18 years of age) were enrolled at 22 sites in Belgium and the Netherlands. Participants had moderately to severely active CD with a CD activity index (CDAI) between 220 and 450 at screening and with objective evidence of ulcerations at baseline endoscopy. Patients who previously failed or were intolerant to TNF antagonist or those naïve to these agents were eligible. Following screening, patients received open-label intravenous treatment with 300 mg VDZ at weeks 0, 2, and 6 (induction treatment), followed by maintenance treatment with 300 mg VDZ every 8 weeks. An additional VDZ infusion was given at week 10 to patients who had no clinical response, defined as failure to achieve a >70-point CDAI decrement from baseline. Patients received treatment with VDZ for 1 year, which was the time point of the final assessment. All background CD medication was kept stable during the trial except for corticosteroids, which were tapered once clinical response was attained until complete withdrawal by week 26, if possible. Patients were considered in clinical remission only if their CDAI score was <150 with complete withdrawal of corticosteroids. All patients provided written informed consent. The study protocol was approved by the investigational review board at each study center. All authors had access to the study data and reviewed and approved the final manuscript.

Procedures

Assessments included physical examination, monitoring of laboratory data including C-reactive protein (CRP), CDAI scoring, and recording of adverse events at baseline and before every infusion. Serum was analyzed for VDZ concentrations and anti-VDZ antibodies (AVA) before every infusion in the first 26 weeks. Ileocolonoscopies were performed and video-recorded by experienced endoscopists (site readers [SRs]) at baseline and weeks 26 and 52. The Simple Endoscopic Score for Crohn's Disease (SES-CD), which evaluates size of ulcers, ulcerated surface, affected surface, and presence of stenosis in 4 segments of the colon and in the terminal ileum, was used for scoring. Total scores range from 0 to 56 points, with higher scores reflecting more severe disease.[16] Patients who withdrew from the study before week 26 or week 52 had an exit endoscopy. Video recordings were also centrally reviewed by 4 expert CRs who were unaware of the study visit sequence or clinical information. The CR score was used for final analysis except when CR and SR scoring were discrepant, defined as follows. If the SR SES-CD was 0 to 3, a 1-point difference between SR and CR was considered a discrepancy. For SR SES-CD 4 to 7, 8 to 15, and ≥16, a difference >2 points, >3 points, and >4 points between SR and CR was considered to represent discrepancy.[17] Videos with discrepant reads were sent for adjudication by 2 other members of the CR team in an adjudication meeting, during which the video and the previous scores were evaluated. The SR or CR score closest to the adjudication read was used for further analysis.

Mucosal biopsies were obtained at baseline and at week 26. Biopsies were collected from the edge of the most prominent ulcer in each segment (ie, ileum, ascending colon, transverse colon, descending colon and sigmoid, and rectum), or from the most severely affected area if no ulcers were present. If a segment was completely normal, 2 biopsies were taken at random per segment. Biopsies were stored in formalin and subsequently embedded in paraffin. The paraffin blocks were sectioned and stained with hematoxylin and eosin. Histological disease activity was scored blinded by an experienced

pathologist using the Geboes Score (GS)[18] and the Robarts Histopathology Index (RHI).[19] The GS is a 7-item scale (with 4 levels of severity for each item) that categorizes inflammation as grade 0 (architectural change only), grade 1 (chronic inflammation), grade 2 (2a, lamina propria eosinophils and 2b, lamina propria neutrophils), grade 3 (neutrophils in the epithelium), grade 4 (crypt destruction), or grade 5 (erosion or ulceration). The score ranges from 0 to 5.4. The RHI is a 4-item index (with 4 levels for each item) that evaluates chronic inflammation, lamina propria neutrophils, neutrophils in the epithelium, and erosion or ulceration. Total score ranges from 0 to 33, where higher scores denote more severe inflammation. Associations between endoscopic remission (using SES-CD scores per segment; ie, terminal ileum, right colon, transverse colon, left colon, and rectum) and histological remission (using GS and RHI scores per segment) at week 26 were studied, as well as associations between clinical remission and both endoscopic and histological remission.

VDZ Serum Concentrations and AVAs

VDZ serum concentrations were measured at weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, and 52 using an immunoassay using rabbit AVAs to capture VDZ and rabbit anti-VDZ F(ab')2 fragments, as previously described (Sanquin Laboratories, Amsterdam, the Netherlands).[20] The lower limit of quantification in serum is 100 ng/mL; interassay precision and accuracy are 1% to 4% and 87% to 115%, respectively. AVAs were also measured as previously described.[21,22] The lower limit of detection was based on mean >3 standard deviations measured in a panel of 30 sera from healthy donors and 45 sera from patients with inflammatory bowel disease who were treatment naïve for VDZ.

Endpoints and Definitions

Clinical outcomes were clinical response (>70-point decrement in CDAI from baseline) and corticosteroid-free clinical remission (CDAI <150 points and no corticosteroid use). Biochemical remission was defined as a serum CRP concentration <5 mg/L measured in patients with increased CRP at the start of the study. Endoscopic remission and response were defined as a SES-CD score <4 and a $\geq 50\%$ reduction score compared with baseline, respectively.[23,24] Histological remission was defined as GS <3.1 (which correlates with absence of neutrophils in the epithelium)[18,25,26] and an RHI ≤ 6 (absence of granulocyte in mucosal biopsies).[19]

Statistical Analysis

Patient characteristics were evaluated using descriptive statistics. All patients who received at least 1 dose of VDZ were included in the analysis. For patients who withdrew from the study before week 26 or week 52, the exit endoscopy score was analyzed. Missing VDZ serum concentrations were not imputed. VDZ concentration data were compared between patients with and without endoscopic remission and response, using the Wilcoxon-Mann-Whitney test. Fisher's exact test was used to compare endoscopic outcomes at week 26 across VDZ quartiles at week 22. Optimal cutpoints of VDZ concentrations associated with endoscopic outcomes were determined using receiver operating characteristic (ROC) curve analysis. Correlations among clinical, endoscopic, and histological outcomes were

calculated using Pearson correlation for binary outcome (ϕ coefficient). Subgroup analyses were performed to assess how sensitive endoscopic remission rates at weeks 26 and 52 were to variations in the study population. Endoscopic remission at weeks 26 and 52 were stratified by anti-TNF use (anti-TNF naïve vs anti-TNF exposed patients), corticosteroid use at inclusion (<20 mg vs ≥ 20 mg/d) and baseline CRP concentrations (<5 mg/L vs ≥ 5 mg/L). All statistical testing was performed at the .05 significance level using R version 3.4.3 (R Foundation for statistical computing, Vienna, Austria).

Results

Patient Disposition and Demographics

The disposition of the patients is shown in Supplementary Figure 1. Data from 110 participants were analyzed. Seventy-six patients completed week 26 of the study, and 74 of 76 underwent the week 26 endoscopy. Sixty-three patients completed week 52 and 61 of 63 had an endoscopic assessment at that time point. Fourteen patients of 34 early withdrawals before week 26 underwent an exit endoscopy at a median time point of 22.5 weeks. One patient of 11 early withdrawals between weeks 26 and 52 underwent an early withdrawal endoscopy, which was performed at week 28. In total, 260 endoscopic procedures were analyzed. Of these 260 videos, 69 needed a second review because of discrepant reads between SR and CR. The mismatch rate in SES-CD scores between SR and CR was 27% (69/260).

Patient characteristics and demographics are summarized in Table 1. The mean baseline CDAI score was 261, and the mean SES-CD score was 12. Nine (8%) of 110 patients had actively draining fistulas at baseline and all fistulas were perianal. In these 9 patients, the rectum was inflamed (according to the SES-CD score) in 2 patients, and both patients did not show endoscopic improvement in the rectum at week 26 or at week 52. In these 2 patients, there were no changes observed regarding fistula drainage (assessed clinically) at both time points. For all 9 patients, endoscopic remission was observed in 33% (3/9) and 22% (2/9) at week 26 and 52, respectively. Fistula closure, as assessed clinically, was observed in 3 of 9 patients during 52 weeks of follow-up. Concomitant treatment with corticosteroids and immunosuppressives was present in 41% and 20% of patients at study entry, respectively, and 88% had previously been treated with TNF antagonists. Twenty patients (18%) of 110 were using prednisone at baseline, 8 of whom received "high" prednisone doses defined as ≥ 20 mg/d. Sixty-eight percent of patients (75/110) had elevated CRP levels (≥ 5 mg/L) at baseline. Sixty-four percent (70/110) of patients received an additional infusion with VDZ at week 10 because of lack of clinical response.

Clinical Outcomes

Corticosteroid-free clinical remission was observed in 32 (29%) of 110 patients at week 26 and in 34 (31%) of 110 at week 52 (Figure 1). Clinical response was present in 42 (38%) of 110 patients at week 26 and in 39 (35%) of 110 at week 52 (Figure 1). The mean drop in CDAI score from

Table 1. Patient Characteristics at Baseline

Total	110
Age, y	36 (28–46)
Female, n (%)	77 (70)
BMI, kg/m^2	24 (22–27)
Smoking status	
Current smoker	30 (27)
Ex-smoker	33 (30)
Never smoked	47 (43)
Age at diagnosis, yr	23 (19–34)
Disease duration, yr	9 (5–16)
Disease location, n (%)	
Ileitis	26 (24)
Colitis	32 (30)
Ileocolitis	50 (46)
Draining fistulas, %	9 (8)
Prior anti-TNF therapy, n (%)	97 (88)
High sensitive CRP, mg/L	9 (4–22)
Elevated CRP at baseline, n (%)	75 (71%)
Serum albumin (g/dL)	42 (38–44)
CDAI	261 (238–312)
SES-CD	12 (7–17)
Concomitant corticosteroids, n (%)	45 (41)
Concomitant immunomodulators, n (%)	22 (20)

NOTE. values are median (interquartile range) or n (%).
BMI, body mass index.

baseline to week 26 and 52 was 131.52 and 124.83 points, respectively. CDAI outcomes (ie, proportion of patients with clinical remission and response) and normalization of CRP concentrations (CRP <5 mg/L) at all time points are presented in Supplementary Figure 2.

Endoscopic and Histological Outcomes

In the nonresponder imputation population (110 patients), endoscopic response was observed in 44 (40%) of 110 patients at week 26 (95% confidence interval [CI] 0.31–0.50) and in 50 (45%) of 110 at week 52 (95% CI 0.36–0.55) (Figure 1). Endoscopic remission was present in 36 (33%; 95% CI 0.24–0.42) and in 40 (36%; 95% CI: 0.28—0.46) of 110 patients at week 26 and week 52, respectively. The mean change in SES-CD scores from baseline to week 26 and 52 were 4.05 and 4.65, respectively. Clinical and endoscopic outcomes in a subset of patients (n = 70) who received an additional week 10 infusion with VDZ are shown in Supplementary Figure 3. The effect of prior exposure to TNF antagonists on these outcomes could not be assessed, because most patients received prior treatment with these agents. Endoscopic remission at week 26 did not differ between terminal ileum and colonic segments (Supplementary Figure 4). The proportion of patients who had documented endoscopic lesions at baseline and achieved endoscopic remission at week 26, was 66%, 62%, 74%, 63%, and 77% in the terminal ileum, ascending colon, transverse colon, descending colon and sigmoid, and rectum, respectively. Endoscopic remission rates at weeks 26 and 52 were analyzed across disease duration quartiles (ie, <5 years, between 5 and 9 years, between 9 and 15.5

years, and >15.5 years). Higher endoscopic remission rates at week 52 were observed in patients with a shorter disease duration compared with patients with a longer disease course (Supplementary Figure 5). This differences was not observed at week 26. Several sensitivity analyses were performed, as shown in Supplementary Figure 6. Eighty-eight percent of patients (97/110) were exposed to prior anti-TNF treatment and endoscopic remission was achieved in 29% (CI 20–39) and 33% (CI 24–43) at week 26 and 52, respectively. Sixty-eight percent of patients (75/110) had elevated CRP levels (≥5 mg/L) at baseline, and in this subgroup endoscopic remission at weeks 26 and 52 was achieved in 25% (CI 16–37) and 28% (CI 19–40), respectively. Eighteen percent of patients (20/110) used prednisone at baseline (8 at high [≥ 20 mg/d] dose). Endoscopic remission was achieved in 25% of prednisone users at baseline at weeks 26 and 52.

Analysis of histologic outcomes was restricted to paired biopsies from all segments collected at week 0 and week 26 with active inflammation at baseline. In total, 132 paired biopsies in 65 patients (ie, collected at week 0 and week 26 obtained from the same segment) were analyzed in which active inflammation was present at baseline. Sixty-seven biopsies had active inflammation at baseline according to the GS (score ≥3.1), and 43 (64%) of 67 showed histological remission (GS <3.1) at week 26 (Figure 2A). Fifty-six biopsies had active inflammation at baseline according to the RHI (score >7), and histological remission (RHI ≤6) was observed in 37 (66%) of 56 biopsies at week 26 (Figure 2A). The mean change in RHI scores from baseline to week 26 was 2.86. Next, correlations between endoscopic and histological remission at week 26 were analyzed. For 125 samples (64 patients), SES-CD and GS outcomes were available that were scored in the same segments. In 88% (78/89) of these samples, which were obtained from patients achieving endoscopic remission at week 26, histological remission was also observed ($\phi = 0.45$). For 130 samples (65 patients), SES-CD and RHI scores were available in the same segments. In 91% (84/92) of these samples achieving endoscopic remission at week 26, histological remission was present ($\phi = 0.46$) (Supplementary Table 1). **Q4** In addition, correlations between clinical remission and endoscopic and histological outcomes were analyzed. Clinical remission was observed in 36% (13/36) of patients who also achieved endoscopic remission at week 26 ($\phi = 0.11$). In 47% (18/38) and 50% (21/42) of patients who achieved clinical remission, histological remission at week 26 was observed using the GS ($\phi = 0.10$) and RHI ($\phi = 0.19$), respectively (Supplementary Table 2).

Pharmacokinetic/Pharmacodynamic Analysis

VDZ serum trough concentrations up to week 22 are depicted in Supplementary Figure 7. The median VDZ serum concentration was significantly higher at all time points except for weeks 2 and 14 in patients who achieved endoscopic remission than in those who did not (Figure 3). In patients with and without endoscopic remission, median VDZ serum concentrations were 28 and 26 mg/L at week 2

Figure 1. Proportion of patients achieving steroid-free clinical remission (CDAI <150), clinical response (at least 70-point drop in CDAI compared with baseline), endoscopic remission (SES-CD <4) and endoscopic response (50% reduction in SES-CD compared with baseline) at week 26 and week 52. Proportions were determined in nonresponder imputation population (n = 110).
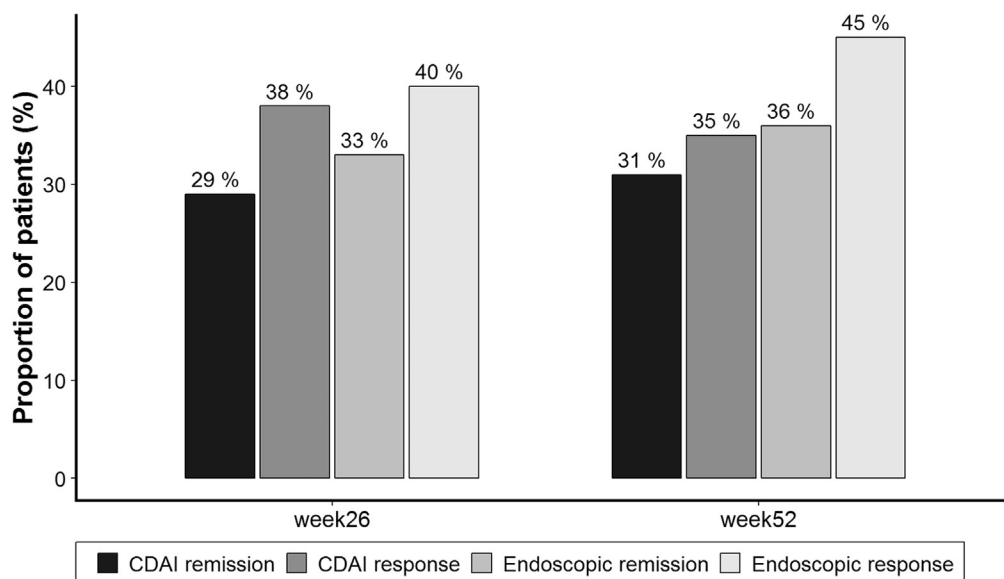

$(P = .12)$, 31 and 25 mg/L at week 6 $(P = .01)$, 31 and 26 mg/L at week 10 $(P = .04)$, 25 and 22 mg/L at week 14 $(P = .29)$, and 18 and 11 mg/L at week 22 $(P = .0005)$. Similarly, patients with endoscopic response at week 26 had significantly higher median VDZ concentrations at these same time points (Figure 3C). Median VDZ serum concentrations were 27 and 26 mg/L at week 2 $(P = .43)$, 31 and 24 mg/L at week 6 $(P = .02)$, 31 and 25 mg/L at week 10 $(P = .02)$, 26 and 21 mg/L at week 14 $(P = .10)$, and 17 and 11 mg/L at week 22 $(P = .01)$ in patients with and without endoscopic response, respectively.

In addition, the concentration-effect relationship between VDZ serum concentrations at week 22 (ie, serum concentration at trough closest to the week 26 colonoscopy) and endoscopic outcomes at week 26, were analyzed by quartile analysis (Figure 4). Higher VDZ serum concentrations at week 22 were associated with higher rates of endoscopic remission (Figure 4A) and endoscopic response (Figure 4B). Endoscopic remission rates at week 26 were

16%, 56%, 47%, and 75% among patients in quartile 1 through quartile 4, respectively $(P = .004)$. Endoscopic response rates at week 26 were 32%, 56%, 58%, and 75% among patients in quartile 1 through quartile 4, respectively $(P = .08)$.

The area under the ROC curve, quantifying associations between VDZ serum levels at week 22 and endoscopic remission and response at week 26, is shown in Figure 5. A VDZ serum concentration above the cutoff level of 10 mg/L at week 22 correlated with endoscopic remission. A VDZ cutoff serum concentration of 10 mg/L at week 22 was identified that best discriminated patients with and without endoscopic remission at week 26, with an area under the curve of 0.74, a sensitivity and specificity of 0.91 and 0.54, respectively, a positive predictive value of 64%, and a negative predictive value of 87% (Figure 4C). A VDZ threshold concentration of 10.5 mg/L at week 22 discriminated patients with and without endoscopic response at week 26 with an area under the curve of 0.69 with a

Figure 2. (A) Proportion of biopsies with histological remission at week 26, defined as GS <3.1 and RHI ≤6. Paired biopsies (week 0 and week 26) were analyzed with documented active inflammation at baseline. (B) Histologic images before treatment with VDZ, showing colonic mucosa with active inflammation and ulceration (top), and 26 weeks following VDZ treatment (bottom) showing normal colonic mucosa.
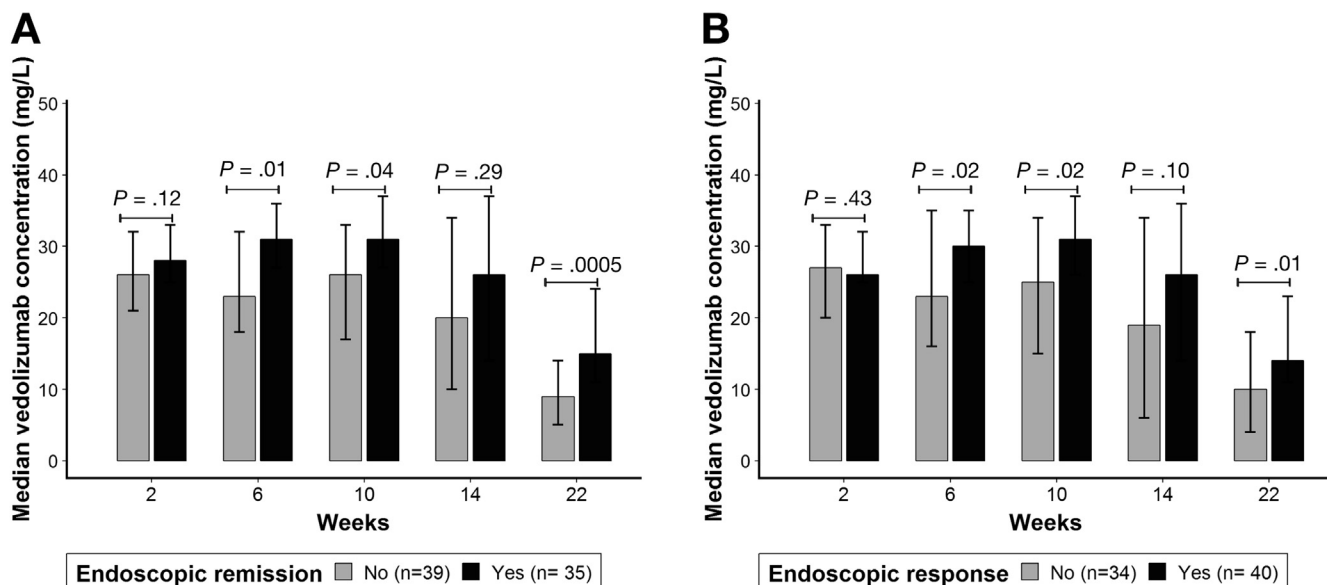

print & web 4C/FPO
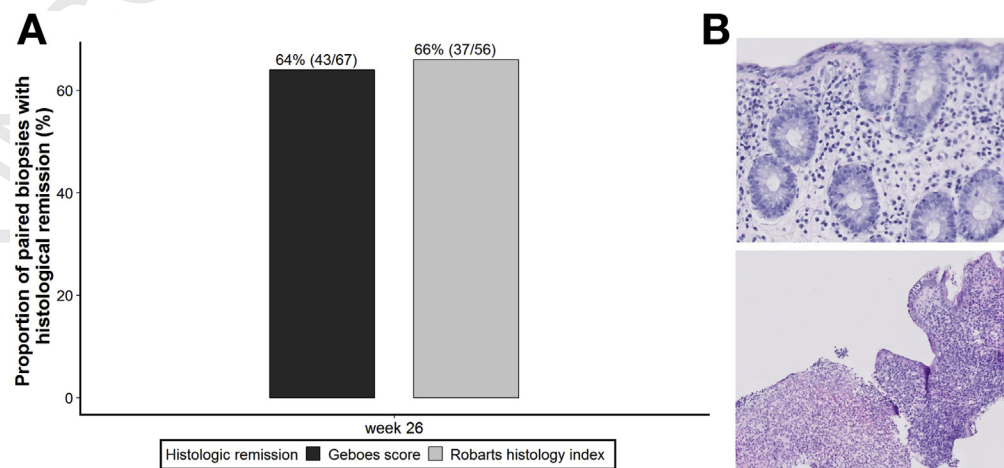
Figure 3. (*A*) Median VDZ serum concentrations at different time points among patients who did (*blue*) or did not (*red*) achieve endoscopic remission (SES-CD <4) at week 26. (*B*) Median VDZ serum concentrations at different time points among patients with (*blue*) and without (*red*) endoscopic response (decrease in SES-CD >50%) at week 26. Seventy-four procedures were performed at week 26. *P* values were calculated based on Wilcoxon-Mann-Whitney test.

positive predictive value and negative predictive value of 69% and 70%, respectively, with a sensitivity of 0.79 and a specificity of 0.59 (Figure 4*D*). Supplementary Tables 3 and 4 show correlations between VDZ serum concentrations at week 2, week 6, and week 14 and endoscopic remission and response at week 26.

Immunogenicity

The proportion of patients with detectable AVA at different time points throughout the study varied between

1% and 4% (Supplementary Table 5). All patients with AVA had measurable VDZ serum concentrations; median VDZ serum concentrations in patients with detectable AVA were 26, 26, 26, 21.5, and 12 mg/L at week 2, week 6, week 10, and week 22, respectively. AVA disappeared in all patients except for 1 patient who had detectable AVA up to week 52, but VDZ treatment was not discontinued in this patient. One patient with detectable AVA discontinued VDZ treatment before week 26, because of insufficient clinical and endoscopic response.
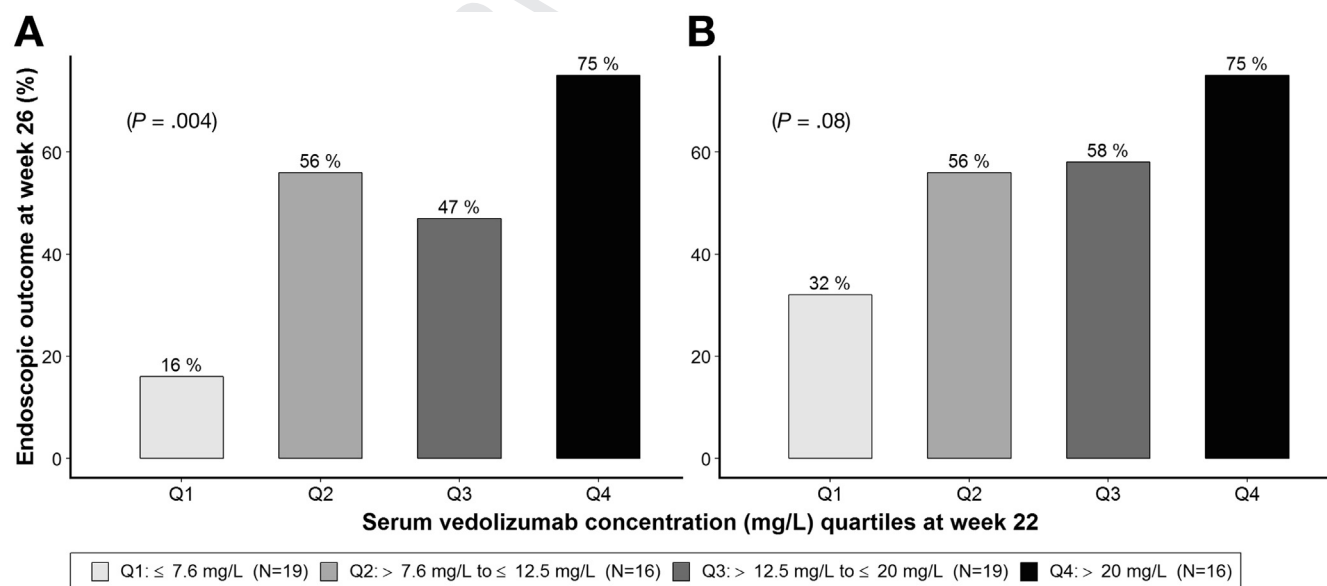
Figure 4. (*A*) Proportion of patients achieving endoscopic remission at week 26 by serum VDZ concentration quartile at week 22. (*B*) Proportion of patients achieving endoscopic response at week 26 by serum VDZ concentration quartile at week 22. Q, quartile.
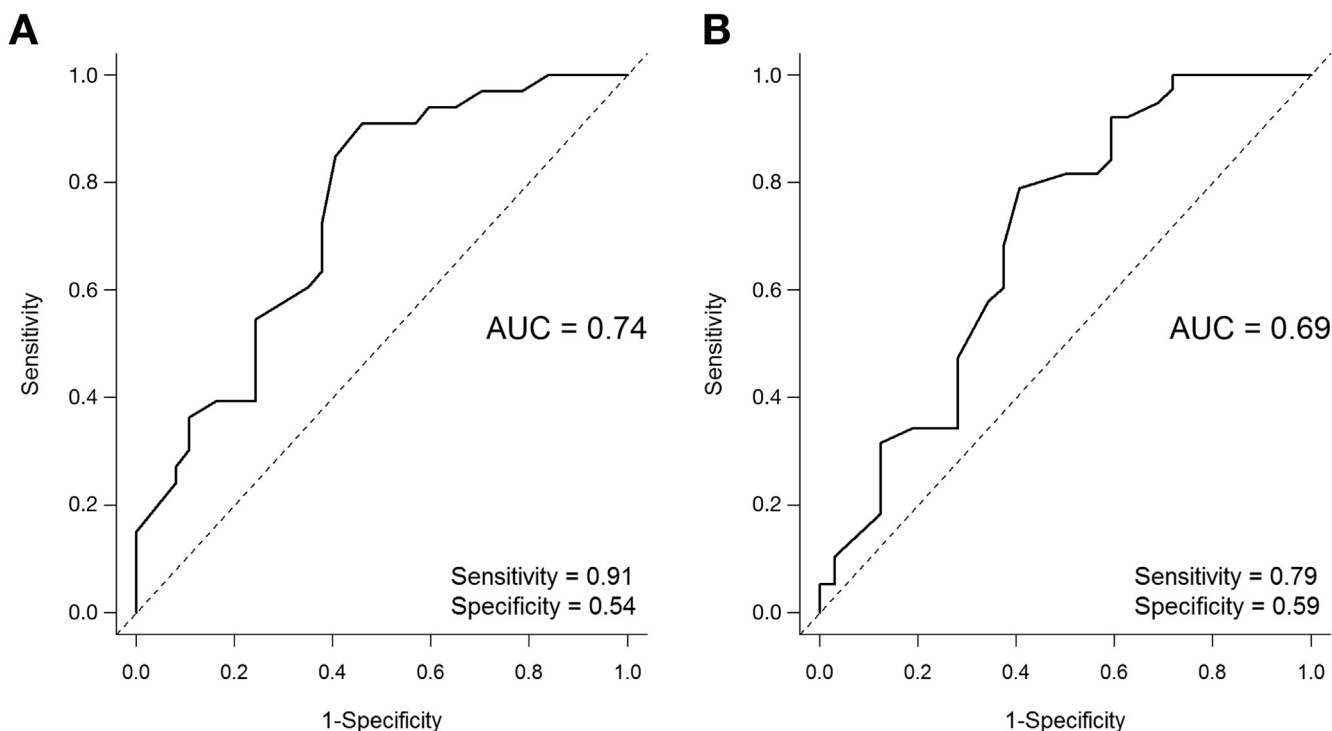
Figure 5. (*A*) ROC curve analysis: correlations between VDZ serum levels at week 22 and endoscopic remission at week 26. (*B*) ROC curve analysis: correlations between VDZ serum levels at week 22 and endoscopic response at week 26. AUC, area under curve.

Safety

Adverse events that occurred in at least 5% of patients receiving VDZ are listed in Supplementary Table 6. Skin-related problems, headache, and nasopharyngitis were among the most frequently reported side effects. Two serious adverse events were reported. One patient underwent a subtotal colectomy with ileosigmoidal anastomosis because of an intestinal stenosis and 1 patient was admitted for worsening of symptoms consistent with a flare of CD. Three of 110 patients discontinued treatment because of side effects. No cases of *Clostridium difficile* were observed. Twenty-five of 110 patients reported arthralgia/arthritis complaints (21 were classified as mild, 4 as moderate) by week 52, and 4 of 25 were reported as related to VDZ. There were 5 reports of worsening of arthralgia, 2 of 5 were reported as related to the treatment.

Discussion

The patients evaluated in LOVE-CD were a difficult-to-treat population with an average disease duration of 9 years. Furthermore, most participants (88%) had previously failed treatment with TNF antagonists. Corticosteroid-free clinical remission was observed in 29% and 31% of these patients following 26 and 52 weeks of VDZ therapy, respectively, and clinical response was present in 38% and 35% at these time points. By way of comparison, in GEMINI 3, 27% of TNF-exposed patients achieved clinical remission by week 10. Thus, our findings are consistent with previously published data on the beneficial effect of VDZ induction therapy on clinical disease activity in CD.

Using a stringent endoscopic assessment protocol at prespecified time points and based on a nonresponder imputation analysis, endoscopic remission (SES-CD <4) was observed in 33% of the patients at week 26 and in 36% at week 52. Corresponding rates of endoscopic response, defined as ≥50% reduction in SES-CD, were 40% and 45%. Interestingly, endoscopic remission rates did not increase substantially between week 26 and week 52 despite continued treatment with VDZ every 8 weeks. This is somewhat similar to the outcome of EXTEND, in which almost identical endoscopic remission rates were reported at weeks 12 and 52 on adalimumab treatment.[27] Based on these observations, it is possible that a finite period is needed to induce mucosal improvement, after which no further healing is attained. However, to further investigate this hypothesis, clinical trials with longer follow-up, optimized pK, and repeated endoscopies beyond 1 year are needed.

Endoscopic disease severity in LOVE-CD was assessed independently by SRs and CRs according to a stringent adjudication algorithm. Although LOVE-CD was an open-label trial, which is a limitation of the study, CRs were unaware of the time point of the endoscopy and had no knowledge of the clinical status of patients. Accordingly, we believe that these measures generated unbiased estimates of the beneficial effects of VDZ on mucosal inflammation. It should be noted that these estimates are higher than those derived in the VERSIFY trial, an open-label study of VDZ in CD that also featured blinded evaluations of SES-CD scores by CRs.[28] In VERSIFY, the endoscopic remission rate at weeks 26 and 52 was 12% and 25%, respectively. Several

protocol and patient population factors may account for these differences. Most importantly, in LOVE-CD dose intensification, consisting of administration of a week 10 VDZ infusion, was specified by the protocol if clinically relevant improvement in disease activity was not observed at that time. This finding should lead to further controlled studies of intensification of VDZ induction therapy in treatment-resistant patients.

It is relevant to consider that the results of these 2 open-label studies can be benchmarked against estimates derived from a recent meta-analysis of placebo-controlled trials that used SES-CD to define endoscopic remission and response rates. In this study, the pooled endoscopic remission and response rates using the same definitions used in LOVE-CD and VERSIFY were 5.2 (95% CI 1.7%–8.8%) and 16.2% (95% CI 10.5%–22%), respectively (Duijvestein M et al, manuscript submitted to *Clinical Gastroenterology and Hepatology*). Thus, the endoscopic rates of remission and response were approximately twice those expected with placebo. In contrast, a recently reported open-label trial of mongersen, an antisense oligonucleotide against Smad7 performed in patients with moderate to severe CD, reported remission and response rates, using the same SES-CD definitions, of only 4% and 15% of patients, respectively.[29] Subsequently, the mongersen development program was terminated following an interim analysis of the results of 2 independent placebo-controlled trials that showed no benefit of the drug on either clinical or endoscopic outcome. Collectively, these effects on mucosal inflammation observed in LOVE-CD were the results of VDZ therapy and not due to regression to the mean or the presence of concomitant therapy.

Although indirect comparisons between these results and those obtained for other drug classes should be interpreted with considerable caution, they are unavoidable in the absence of comparative effectiveness trials. The endoscopic remission rate of 33% at week 26 and 36% at week 52 that we report in the current study compares favorably with those reported in clinical trials with other treatments for CD. In the EXTEND trial with adalimumab, 27% and 24% of the patients had no ulcerations at week 12 and 52, respectively.[27] In the SONIC trial, patients also had an endoscopic evaluation at week 26 and a less refractory population of patients with CD was studied, because they were all naïve to immunosuppressive agents and biologics at study entry.[30] In this study, "absence of ulcers" was observed in 30% on infliximab monotherapy and in 44% on combination treatment. More recently the IMMUNITI investigators reported endoscopic remission and response rates of 13% and 17% following 44 weeks of ustekinumab therapy in a group of patients with a moderately high rate of previous failure to TNF antagonists who had responded to ustekinumab induction therapy.[31] Finally, in a recent trial of risankizumab, a novel antibody directed against the p19 subunit of interleukin 23, relatively higher doses of antibody (600 mg every 4 weeks) were administered during 2 consecutive induction phases followed by 180 mg every 8 weeks subcutaneously.[32] After 1 year of treatment, endoscopic remission was seen in 52% of the patients, which

appears considerably higher than with ustekinumab. Whether it is the selective interleukin 23 inhibition or the more optimal exposure regimen that explains this difference remains to be clarified.

Collectively, this experience shows that endoscopic remission and response rates are relatively low even with our best investigational and established treatments, and that early treatment in biologically naïve patients provides the greatest opportunity for success. Further research into strategies for improving mucosal healing rates is a research priority. In this regard, our data evaluating drug concentrations is of interest. Overall, we found higher endoscopic remission and response rates in patients with higher serum concentrations, except for endoscopic outcomes at week 14, in which no significant differences in serum levels were found between patients with and without endoscopic remission and response at week 26. This can be explained by the fact that week 14 VDZ serum concentrations came from patients with and without an additional week 10 infusion (64% vs 36%, respectively). Endoscopic outcomes at week 26 were notably greater in the 3 highest quartiles of VDZ exposure than in the first quartile. Quartile analysis of exposure at week 22 indicated that a drug concentration above 7.6 μg/mL was associated with endoscopic healing; however, it remains to be determined whether this relationship is causal and if dose intensification will lead to better endoscopic outcomes. Hence, future prospective dose-optimization studies will have to prove if dose intensification can further improve outcomes. In addition, ROC curve analysis identified a VDZ serum cutoff level of 10 mg/L at week 22 that correlated with optimal endoscopic outcomes at week 26, with a high sensitivity (0.91), but with a rather low specificity (0.54). Correlations between VDZ serum concentrations at earlier time points (weeks 2, 6, and 14) and endoscopic outcomes at week 26 were less evident, suggesting that TDM may be useful only during maintenance therapy with VDZ.

Based on sensitivity analyses, no firm conclusions can be drawn as to which patient subgroups the observed outcomes apply. This is because most patients failed on prior anti-TNF treatment, prednisone was used in only 18% of patients at inclusion, and baseline CRP levels were elevated in most patients. We could not stratify patient outcomes based on estimates of disease burden, such as stool markers of inflammation or disease extent at imaging, because these analyses were not part of the study protocol.

Although endoscopic remission is associated with better outcomes in CD, less is known about the clinical relevance of achieving histological remission, which is emerging as a novel endpoint in clinical trials.[33] Furthermore, endoscopic remission is not always paralleled by histological remission.[34] Although validated definitions for histological remission in CD are lacking,[35] we believe that we used the best available scores determined by a central independent reader. Histological remission, an outcome not previously reported in VDZ studies in CD, was observed in 64% and 66% of paired biopsies at week 26. Interestingly, in approximately 90% of samples, a correlation was found between endoscopic and histological remission at week 26.

Hence, these findings highlight the fact that VDZ is able to induce histological remission in endoscopic responders in CD. Whether histological remission will result in improved long-term outcomes needs to be defined.

Between 1% and 4% of patients had detectable AVA at different time points throughout the study. Of note, AVAs seem to be transient in most cases, unrelated to clinical outcomes and they did not impact VDZ serum concentrations. From these observations, it can be concluded that determination of AVA is not clinically useful with the assay that we used, which is in line with observations by others.[36–38]

In conclusion, this study shows that VDZ is effective in achieving endoscopic and histological remission in CD, and improved endoscopic outcomes are associated with higher VDZ serum concentrations.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.05.067.

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Supplementary Figure 1. Consort diagram: patient flowchart during the study.
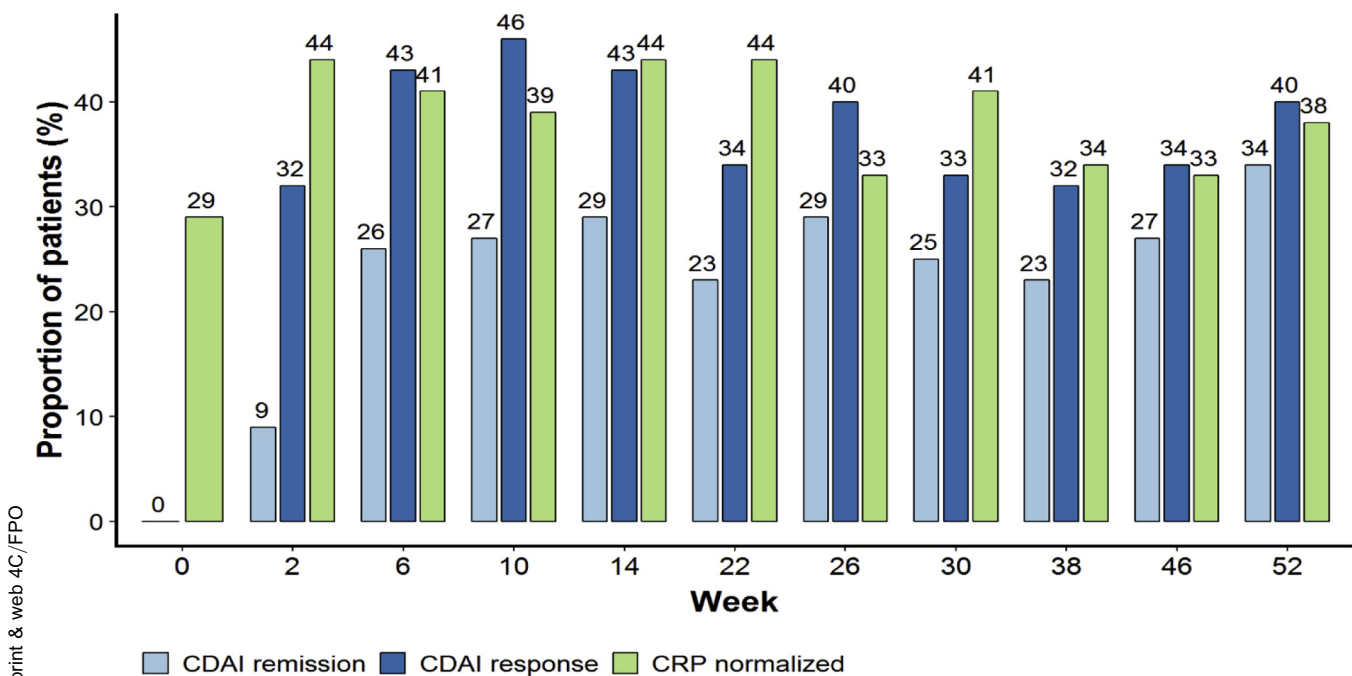
Supplementary Figure 2. CDAI response/remission and CRP concentrations at all time points (ITT).
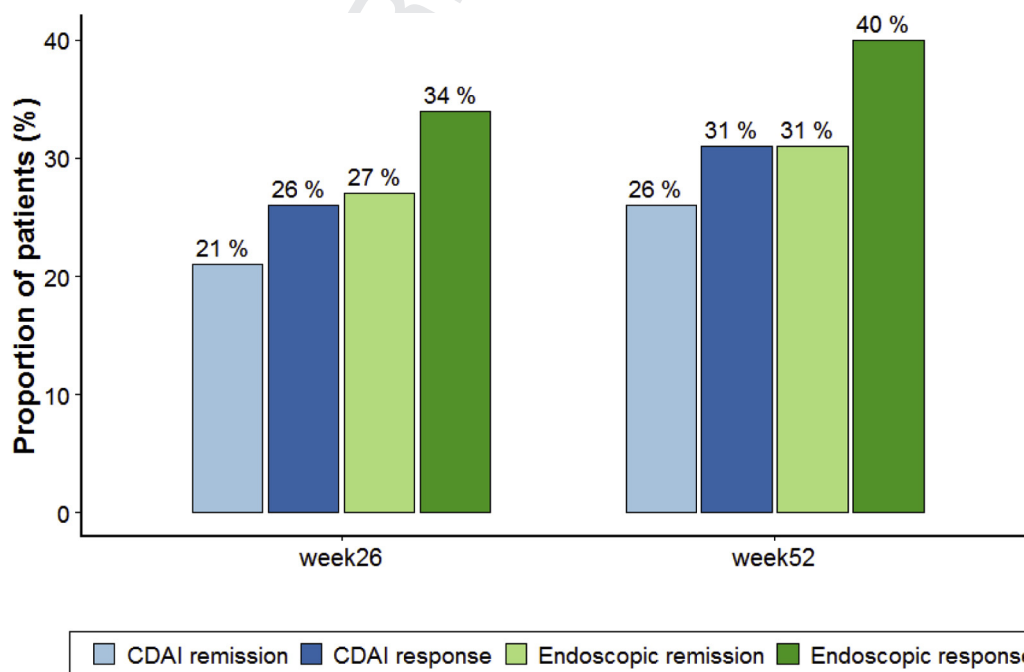
Supplementary Figure 3. Corticosteroid-free clinical remission and endoscopic outcomes in patients receiving additional week 10 infusion.
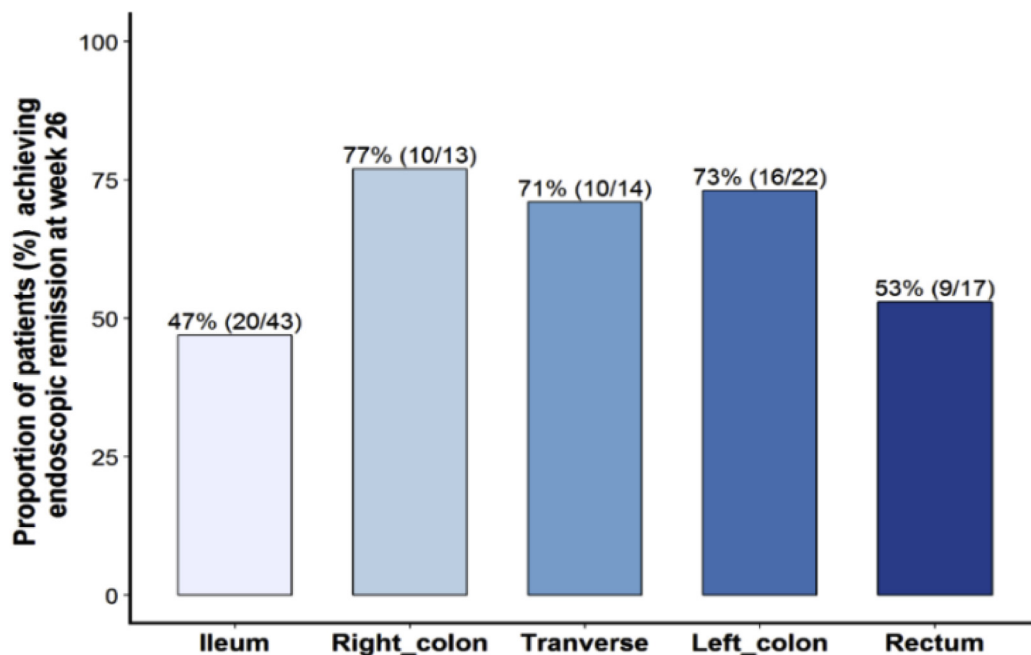
Supplementary Figure 4. Proportion of patients achieving endoscopic remission at week 26 per segment.
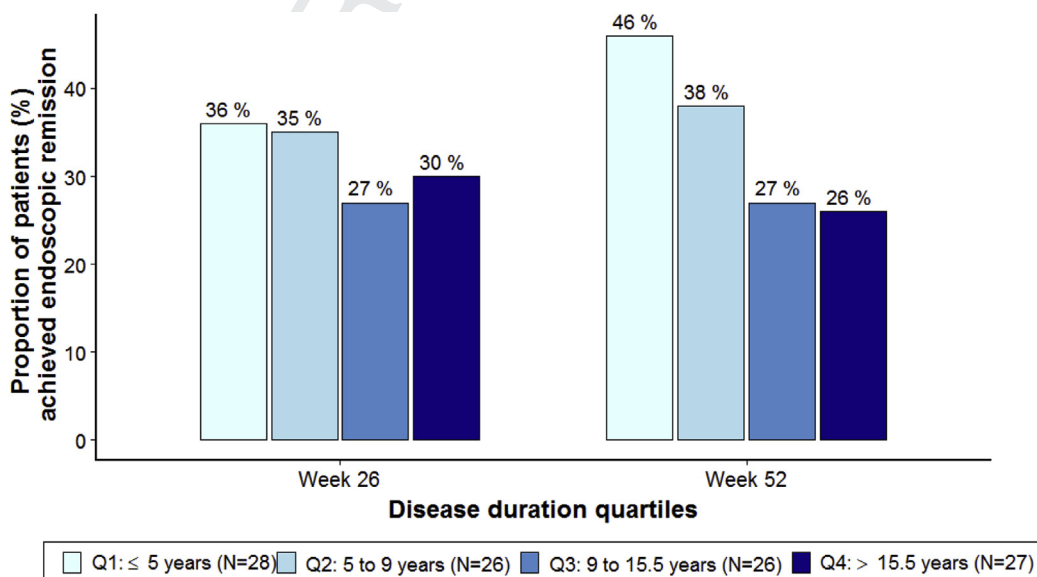
Supplementary Figure 5. Proportion patients achieving endoscopic remission at week 26 and week 52 across disease duration quartiles. Q, quartile.

Proportion (%) of patients achieving endoscopic remission at week 26 and 52

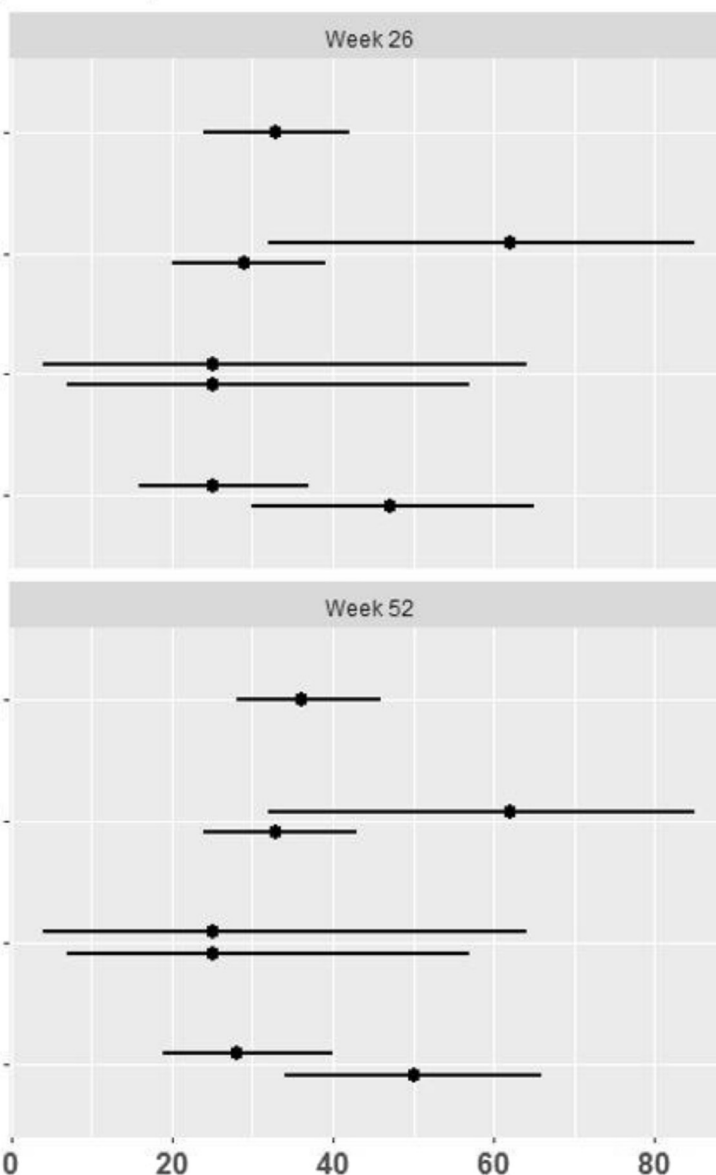| Population	n	N	(%)	95% CI
All patients	36	110	33	(24,42)
Anti-TNF				
Naive	8	13	62	(32,85)
Exposed	28	97	29	(20,39)
Prednisone use				
≥ 20 (mg/d)	2	8	25	(4,64)
< 20 (mg/d)	3	12	25	(7,57)
Baseline CRP				
≥ 5 (mg/L)	19	75	25	(16,37)
< 5 (mg/L)	15	32	47	(30,65)
All patients	40	110	36	(28,46)
Anti-TNF				
Naive	8	13	62	(32,85)
Exposed	32	97	33	(24,43)
Prednisone use				
≥ 20 (mg/d)	2	8	25	(4,64)
< 20 (mg/d)	3	12	25	(7,57)
Baseline CRP				
≥ 5 (mg/L)	21	75	28	(19,40)
< 5 (mg/L)	16	32	50	(34,66)

Supplementary Figure 6. Proportion (%) and 95% confidence interval of patients achieving endoscopic remission at week 26 (upper panel) and week 52 (lower panel) in the total cohort and stratified by prior anti-TNF use, prednisone use at inclusion, and baseline CRP concentrations.
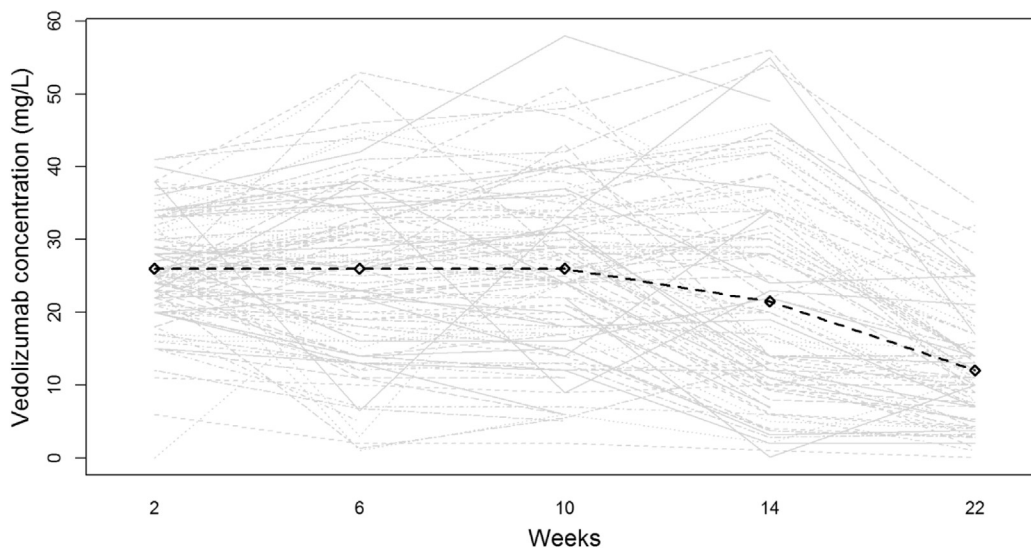
Supplementary Figure 7. VDZ concentrations over time.

Supplementary Table 1. Associations Between Endoscopic and Histological Remission Using the GS and RHI

		Histological remission (GS) week 26, n (%)		Histological remission (RHI) week 26, n (%)	
		No	Yes	No	Yes
Endoscopic remission week 26	No	20 (65)	16 (17)	19 (70)	19 (18)
	Yes	11 (35)	78 (83)	8 (30)	84 (82)
Total		31	94	27	103

Supplementary Table 2. Correlations Among Clinical, Endoscopic, and Histological Remission at Week 26

		Endoscopic remission week 26, n (%)		Histological remission (RHI) week 26, n (%)		Histological remission (GS) week 26, n (%)	
		No	Yes	No	Yes	No	Yes
Clinical remission week 26	No	55 (74)	23 (64)	16 (70)	21 (50)	17 (63)	20 (53)
	Yes	19 (26)	13 (36)	7 (30)	21 (50)	10 (37)	18 (47)
Total		74	36	23	42	27	38

Supplementary Table 3. ROC Curve Analysis: Different Cutoff Values for Endoscopic Remission at Week 26

Week	Cutoff	Specificity	Sensitivity	Accuracy	NPV	PPV	*P*
2	23.5	0.36	0.86	0.59	0.74	0.55	.06
6	25.5	0.59	0.82	0.69	0.79	0.63	.006
14	21.5	0.57	0.62	0.59	0.62	0.57	.1
22	9.9	0.54	0.91	0.71	0.87	0.64	.0002

NOTE. *P* value is related to the area under curve (AUC).
NPV, negative predictive value; PPV, positive predictive value.

Supplementary Table 4. ROC Curve Analysis: Different Cutoff Values for Endoscopic Response at Week 26

Week	Cutoff	Specificity	Sensitivity	Accuracy	NPV	PPV	AUC	P
2	30.5	0.38	0.72	0.57	0.54	0.58	0.55	.2
6	19.5	0.44	0.92	0.71	0.82	0.67	0.67	.01
14	6.05	0.27	1	0.66	1	0.61	0.57	.05
22	10.5	0.59	0.79	0.7	0.7	0.69	0.69	.003

NOTE. *P* value is related to the area under curve (AUC).
NPV, negative predictive value; PPV, positive predictive value.

Supplementary Table 5. Detectable AVAs

Week	Nondetectable AVA (numbers)	Detectable AVA (numbers)	Detectable AVA (%)
0	102	1	1
6	104	4	4
10	103	2	2
14	94	1	1
22	82	1	1
38	58	0	0
46	57	0	0
52	64	1	1

Supplementary Table 6. Adverse Events Reported by More Than 5% of Patients   Q12

Adverse event	n (%)
Skin lesions[a]	16 (15)
Headache	13 (12)
Nasopharyngitis	11 (10)
Arthralgia	6 (5.5)
Nausea	6 (5.5)
Any serious adverse event[b]	2 (1.8)