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

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Ver(s)ifying the Efficacy of Vedolizumab Therapy on Mucosal Healing in Patients With Crohn's Disease

See "Endoscopic, radiologic, and histologic healing with vedolizumab in patients with active Crohn's disease," by Danese S, Sandborn WJ, Colombel J-F, et al, on page 1007; and "Vedolizumab induces endoscopic and histological remission in patients with Crohn's disease," by Löwenberg M, Vermeire S, Mostafavi N, et al, on page 997.

In the past few years, a significant paradigm shift occurred in the management of inflammatory bowel diseases. As advocated by the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)[1] consensus, achieving remission in clinical symptoms alone would not serve as sufficient treatment target; symptoms and patient-reported outcomes should be coupled with objective measures of inflammatory activity. Endoscopy is currently the gold standard for objective assessment of disease activity. More and more emphasis is placed on achieving endoscopic healing as the optimal target for everyday clinical practice and it has also become a major therapeutic end point in clinical trial designs. Fewer data are available about the clinical relevance of histologic remission as a treatment target, especially in Crohn's disease (CD).

Vedolizumab (VDZ) is an anti–$\alpha 4\beta 7$-integrin monoclonal antibody that selectively blocks lymphocyte trafficking into the gastrointestinal mucosa. The pivotal GEMINI 2 and 3 trials demonstrated the clinical efficacy of VDZ in moderate to severe CD; however, they did not provide data on endoscopic healing. Subsequent retrospective evaluations have been published, but little prospective data exist to address this knowledge gap. In the current issue of *Gastroenterology* are 2 prospective clinical trials evaluating endoscopic and histologic healing in VDZ therapy: Danese et al[2] report results of the VERSIFY trial assessing endoscopic remission as primary and histologic and radiological (magnetic resonance enterography) inflammation as secondary end points, and Löwenberg et al[3] present endoscopic and histologic results and data on therapeutic drug monitoring in a prospective open-label trial.

The VERSIFY (NCT02425111)[2] trial is a phase 3b, single-group study of 101 CD patients with moderate to severe disease activity treated by standard regimen VDZ. At weeks 26 and 52, 11.9% and 17.9% of patients in the study population achieved endoscopic remission, respectively (demonstrated by an Simple Endoscopic Score for Crohn's Disease [SES-CD] score of $\leq$4), and 24.8% and 53.6%, respectively, had an endoscopic response ($\geq$50% decrease from baseline SES-CD score). Endoscopic remission rates were consistently lower in patients who did not fail anti-tumor necrosis factor therapy compared with patients naïve to anti-tumor necrosis factor therapy (week 26, 5.5% vs 19.6%). In a secondary analysis, endoscopic improvements were generally greater in the colonic segments than in the ileum at both weeks 26 and 52. The LOw countries VEdolizumab in CD (LOVE-CD) trial[3] evaluated endoscopic data from 110 patients with moderate to severe CD and reported endoscopic remission (SES-CD score of $\leq$3) in 33% and 36% of patients and endoscopic response (decrease in SES-CD score of $\geq$50%) in 40% and 45% of patients at treatment weeks 26 and 52, respectively.

Although the endoscopic remission rates show a notable difference between these 2 studies, comparisons across studies should be interpreted with caution owing to differences in design, definitions, and patient population. Importantly, the LOVE-CD protocol enabled dose intensification in the form of week 10 additional infusion and every 4 week dosing after treatment week 30 if deemed necessary. So far, the largest available dataset on endoscopic outcomes in VDZ therapy came from the VICTORY[4] real-world registry, which estimated endoscopic healing rates of 20% and 63% after 26 and 52 weeks of VDZ therapy, respectively. These rates are considerably higher than that of the VERSIFY and LOVE-CD study; however, VICTORY captured endoscopy data retrospectively and no endoscopic score was used systematically, unlike in the case for VERSIFY and LOVE-CD. This more global evaluation of mucosal healing, can lead to a potential overestimation of efficacy. The remission rates of the VERSIFY and LOVE-CD trials seem low compared with the mucosal healing rates reported in other pivotal trials, for example, the SONIC[5] or EXTEND trials.[6] However, when study design, patient population, and outcome definitions are corrected for by the interpretation, each study confirms clinically important mucosal healing. The SONIC and EXTEND trials define mucosal healing as the absence of ulcerations, a criteria which is probably less stringent than the definitions used in the VERSIFY and LOVE-CD (SES-CD of $\leq$3 or 4). As the authors reported in the VERSIFY trial, when endoscopic outcome definitions are changed to the absence of ulcers, the rate of mucosal healing was significantly higher.

The previous example underscores one of the most important practical aspects and problems of recent clinical trial designs on mucosal healing, which is the absence of widely accepted and validated definitions of endoscopic healing in CD. This leads to the arbitrary choice of endoscopic end points by investigators. How much healing is needed to reach superior clinical long-term outcomes remains uncertain. A post hoc analysis of the SCONIC trial failed to identify an optimal definition for endoscopic healing or remission that would predict long term outcomes.[7] More specifically, mucosal healing and endoscopic response (defined as a decrease from baseline SES-CD or

CDEIS by ≥50%) at week 26 of treatment was associated with steroid-free clinical remission at week 50 in patients with CD. However, further studies are needed to investigate the additional value and best definition of endoscopic healing that would enable clinician to predict long-term disease outcomes. The International Organization for the Study of Inflammatory Bowel Disease, after reviewing technical aspects of scoring systems, achieved consensus on endoscopic definitions of remission and response in CD using a Delphi method.[8] Expert investigators ranked first a greater than 50% decrease in the SES-CD or Crohn's Disease Endoscopic Index of Severity for the definition of endoscopic response, and an SES-CD of 0–2 for the definition of endoscopic remission. Of note, these recommendations are yet to be subjected to thorough validation and prospective testing before being widely incorporated into clinical trial designs.

The VERSIFY and LOVE-CD studies are pioneers in presenting results on histologic healing, which has not been previously reported in any VDZ studies. Histologic evaluation in the VERSIFY based on the Global Histologic Disease Activity Score score showed that 24.4% and 28.3% of patients had a histologic response in the colonic and ileal samples, respectively. IN LOVE-CD, histologic remission at week 26 was observed in 64% and 66% of patients based on the Geboes Score and the Robarts Histopathology Index, respectively. Of note, an analysis of histologic outcomes in the latter study was restricted to paired biopsies from all bowel segments (67 patients). Direct comparison between these results is again difficult. Histologic results have not been used before in CD trials as end points because of the lack of a validated index or tool.[9] Although histologic disease activity assessment in ulcerative colitis has an emerging role in clinical trials (and probably also clinical practice) with recently validated score systems being available (Geboes Score, Nancy Index, Robarts Histopathology Index),[10] the similar application of histologic endpoints in CD is more problematic partly owing to the heterogeneity and patchy location of macroscopic and microscopic disease in CD, which can potentially lead to sampling error. Future investigation is needed to determine whether targeting histologic endpoints in CD has additional value to clinical/biomarker and endoscopic assessment and ultimately to predicting clinical outcomes.

The VERSIFY trial also reports on magnetic resonance imaging activity using the MaRIA score in an exploratory analysis, which proved to be another objective assessment of inflammation in selected CD patients. Interestingly, there was only a weak agreement between endoscopy (SES-CD), histology (Global Histologic Disease Activity Score) and clinical (Crohn's Disease Activity Index) measures in this study, although there was a good agreement between the SES-CD and MaRIA scores, which needs to be further evaluated in additional clinical trials.

Of note, by evaluating therapeutic drug monitoring results as a secondary end point, the authors of the LOVE-CD showed that higher VDZ serum concentrations at week 22 correlated with higher rates of week 26 endoscopic remission (receiver operator characteristic analysis, area under the curve of 0.74; cut-off of 10 mg/L); however, correlation between outcomes and drug levels from earlier time points were less evident. The causality of these observations and the role of therapeutic drug monitoring in VDZ therapy will also need additional investigation.

The present data on the efficacy of VDZ have relevant implications for clinical practice. The VERSIFY and LOVE-CD trials both demonstrated the effectiveness of VDZ in inducing and sustaining endoscopic improvements with a good safety profile. This finding strengthens the role of VDZ as a possible first-line therapeutic option for anti-tumor necrosis factor–naïve patients, especially in colonic CD, considering the higher efficacy rates demonstrated in these patient populations. Data on histologic and radiologic outcomes further strengthen the efficacy signal of VDZ; however, the exact role and additive value of these end points needs further investigation. Validated and widely accepted definitions for endoscopic endpoints in CD are urgently needed, while questions remain around the role of histologic assessment as a meaningful clinical treatment endpoint for CD clinical trials.

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Conflicts of interest
The authors disclose the following: LG: discloses no conflicts, TB has been a peaker or advisory board member for Takeda, Janssen, Abbvie, Merck, Pfizer, Pendopharm, Ferring, Shire. PLL:has been a speaker and/or advisory board member: AbbVie, Arena Pharmaceuticals, Celltrion, Falk Pharma GmbH, Ferring, Genetech, Janssen, Merck, Pharmacosmos, Pfizer, Roche, Shire and Takeda and has received unrestricted research grant: AbbVie, MSD and Pfizer.

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Taking a Closer Look at the Biogeography of the Human Gastrointestinal Microbiome

See "Analysis of transcriptionally active bacteria throughout the gastrointestinal tract of healthy individuals," by Vasapolli R, Schütte K, Schulz C, et al, on page 1081.

The human gastrointestinal tract includes a vast biological territory with several distinct ecosystems along its length. Each ecosystem features unique environmental influences on microbial communities. After more than a decade of the Human Microbiome Project,[1,2] MetaHit[3] and other large-scale human microbiome initiatives,[4] researchers continue to wrestle with the fundamental problem of body sampling fidelity. The key question is whether the sampling strategy at a specific body site leads to meaningful biological or medical insights. Practicing gastroenterologists can readily appreciate the convenience of stool specimens for laboratory evaluation of health and disease status. However, despite the hundreds of manuscripts published using stool specimens as the preferred and convenient "window" into the human gastrointestinal microbiome, we are left with the nagging question. Does a fecal sample provide an adequate window into the composition and collective function of human intestinal microbial communities? To address current knowledge gaps, Vasapolli et al[5] systematically characterized the transcriptionally active microbiota in the oral cavity (saliva), stomach (corpus and antrum), small intestine (duodenum, terminal ileum), and large intestine (ascending and descending colon) from the gastrointestinal tracts of healthy participants (n = 21). Prior studies were limited in size and scope.[6] This study describes relative differences among transcriptionally active microbial communities along the entire human digestive tract. Bacterial communities of the human gastrointestinal tract can be placed in four primary classes based on habitat and *Helicobacter pylori* infection status; healthy upper gastrointestinal tract, *H pylori*–positive upper gastrointestinal tract, lower gastrointestinal tract, and feces (Figure 1).

As previous studies have shown, the oral microbiome contains a distinct microbial community that is clearly distinguishable by bacterial composition from that of the upper and lower gastrointestinal tracts.[2,7] The oral microbiome is characterized by a relative abundance of the genus *Prevotella*. Other studies have found *Prevotella* in the lower gastrointestinal tract in amounts inversely proportional to members of the genus *Bacteroides*.[8] Such a "watershed" boundary was apparent in this study with distinct genera of the phylum Bacteroidetes (including *Prevotella*) in the duodenum and a substantially different set of genera of the same phylum (including *Bacteroides*) in the terminal ileum. The stomach has a clearly distinguishable gastric microbiome,[9] and the authors found that a key driver of microbial composition in the stomach is *H pylori* infection status.[5] Prior studies have indicated the importance of this single gastric pathogen and its impact on gastric microbial composition.[10,11] Disease risk pertaining to peptic ulcer disease and gastric adenocarcinoma may be due to the presence of *H pylori* and relative shifts in community composition. These findings stress the importance of long-term colonization by specific pathogens in shaping bacterial community composition and function. *H pylori* sequences were not found in the lower gastrointestinal tract and in feces, suggesting that *H pylori* does not colonize the lower digestive tract and does not affect microbial composition in the colon. Nevertheless, the authors point out that *H pylori* fecal antigen and DNA testing remain useful in