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EDITORIAL

Vedolizumab (VDZ) for UC and CD: Still Safe and Effective After All These Years

Laura E. Bach[1] · **Sasha Taleban**[1]

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Although monoclonal antibody-based (biologic) drugs aimed at the inflammatory cytokine tumor necrosis factor (TNF) have revolutionized the care of patients with inflammatory bowel disease (IBD) since their introduction in 1998 [1], up to 30% show no response to induction therapy [2, 3]. Furthermore, anti-TNF therapy is associated with an increased risk of serious infections and cancers owing to the fact that this class of drugs was initially developed for the therapy of systemic disorders such as psoriatic arthritis. To address these issues, biologic drugs specifically targeting the gut immune system such as vedolizumab (VDZ) were developed. VDZ inhibits the α4β7 integrin of the gut mucosal addressin cell adhesion molecule 1 (MAdCAM-1), thereby avoiding systemic immunosuppression. The pivotal GEMINI trials showed that VDZ was effective in inducing and maintaining remission in patients with IBD without the increased risk of serious or opportunistic infections [2, 3]. Since those initial studies, several others have attempted to address practical clinical questions such as the sustainability of the clinical response, the need for dosing changes, and VDZ efficacy in Crohn's disease. Moreover, controversy exists within the literature regarding whether VDZ use may result in new or worsening arthralgias [4–6].

VDZ, effective in patients with Crohn's disease (CD) and ulcerative colitis (UC), has good durability in both populations. In a systematic review and meta-analysis of studies published between 2014 and 2017, the rate of clinical remission with VDZ was 32%, 39%, and 46% at week 14 and at months 6 and 12, respectively, in UC patients. In CD, remission rates were slightly less at 30%, 26%, and 30% at the same intervals. Corticosteroid-free clinical remission was achieved in 32% and 42% of UC and 22% and 31% of CD patients at months 6 and 12 [7]. The GETAID group reported the 3-year efficacy and safety of VDZ in the OBSERV-IBD cohort, one of the largest IBD patient groups on VDZ. In their prospective study, VDZ-treated patients with previous inadequate or loss of response or intolerance to conventional therapy or at least one anti-TNF agent had corticosteroid-free clinical remission rates of 62.3% and 44.7% in UC and CD patients, respectively, after 1 year [8].

Though many IBD patients who achieve clinical remission on VDZ at 6 months have ongoing remission at 12 months, for every year thereafter, 10% of CD and UC patients lose response to the drug [8]. A recent systematic review and meta-analysis estimated the loss of response to VDZ to be 47.9 and 39.8 per 100 person-years of follow-up in patients with CD and UC, respectively [9]. Often, to re-induce clinical response or to induce clinical remission, VDZ is administered more frequently. The GETAID group reported that at week 54, 69.2% and 52.1% of CD and UC patients, respectively, had undergone dosing optimization [8]. In the GEMINI long-term safety (LTS) trials, increasing frequency from every 8 to every 4 weeks resulted in clinical response and remission rates of 41% and 28% in UC patients, and 47 and 32% in CD patients, respectively, with similar rates in anti-TNF experienced patients [8]. A review of all pertinent VDZ studies through 2017 found response recaptured in 53.8% of patients after dose intensification [9].

A case series by Varkas et al. [4] initially described new or worsening arthralgias after initiation of VDZ therapy. In their report, they described five cases of new-onset or exacerbated sacroiliitis or peripheral arthritis in patients receiving VDZ for treatment of their IBD. The hypothesis to explain these findings postulated that since α4β7 integrin is a ligand for both MAdCAM-1 and vascular cell adhesion molecule-1 (VCAM-1), inhibition of the former in the gut led to α4β7 migration to the other VCAM-1 expressed regions, namely the joints, leading to inflammatory arthritis.

Since the publication of the compelling hypothesis explaining worsening arthralgias by Varkas et al., further work has shown mixed results. A prospective study reported

✉ Sasha Taleban
staleban@yahoo.com

[1] University of Arizona/Banner University Medical Center, Tucson, AZ, USA

clinical benefit of IBD-associated spondylarthritis in VDZ-treated patients, with no new or exacerbation of arthritis and/or sacroiliitis [4]. Furthermore, a post hoc analysis of the GEMINI trials showed that when compared with placebo, treatment with VDZ reduced the likelihood of new or worsening arthralgias [5]. When comparing anti-TNF exposed and anti-TNF-naïve patients, the former had a greater likelihood of new or worsening arthritis or arthralgias-independent treatment with VDZ or placebo. They associated this finding with withdrawal of corticosteroid therapy, as patients receiving corticosteroids reported worsening joint symptoms following corticosteroid withdrawal regardless of being in the treatment or the placebo group.

In this issue of *Digestive Diseases and Sciences*, Reinglas et al. [10] seek to add to the growing body of real-world data addressing VDZ treatment of IBD patients. In their single-center retrospective study evaluating 130 patients (75 CD, 55 UC), the median duration of VDZ therapy was 65 weeks. At 3, 6, and 12 months, the clinical remission rates with VDZ for CD were 9.1, 26.7, and 29.2%, and 44.2, 71.4, and 77.1% for UC. The steroid-free clinical remission rates among CD and UC patients at 3, 6, and 12 months were 9.4%, 21.1%, and 30% and 38.1%, 51.3%, and 53.1%, respectively. The probability of drug discontinuation in CD was 4.9% and 9.4% at 1 and 2 years. Compared with UC, CD patients required more frequent dose intensification at 1- and 2-year follow-up (64.8/87.9% vs 26.5/35.7%) and diminished efficacy if previously exposed to multiple biologic agents. Low rates of AEs were noted. Specifically, with regard to arthralgias, 18 patients reported arthralgia at baseline, and of those patients, 3 reported resolution and 3 reported worsening of symptoms, whereas the remainder reported no change at 12 months.

These results add to a growing body of literature reporting that biologic-naïve patients receiving VDZ demonstrate improved remission rates and lower rates of dose escalation compared with biologic-experienced patients [7]. Moreover, compared with UC patients, patients with CD have less robust responses to VDZ after dose escalation and have a higher incidence of loss of response and drug discontinuation [7–9]. Collectively, these data suggest that VDZ has greater efficacy in UC compared to CD. Furthermore, VDZ appears to be associated with few serious adverse events. Specifically evaluating arthralgias, studies tying VDZ to spondyloarthropathies (SpAs) and peripheral arthritis have mostly been published as case series [4]. Nevertheless, studies not showing this association were retrospective and not designed to evaluate VDZ-induced arthritis [5]. It is also possible that previous studies on this topic combine multiple distinct forms of arthritis. Therefore, although prior medical therapies (i.e., anti-TNFs and corticosteroids) can mask underlying IBD-associated SpA and peripheral arthritis in some patients who initiate VDZ, other patients may develop VDZ-induced arthritis. Though the current study by Reinglas et al. does not show an association between VDZ and new-onset arthritis, further studies are needed to better define this relationship. Nonetheless, the studies of VDZ efficacy and safety in IBD suggest: (1) lower rates of clinical remission in CD compared to UC, especially if previously exposed to anti-TNF agents, (2) the need to make dose adjustments, particularly in patients with CD, and (3) few serious adverse effects.

The current study increases knowledge regarding the efficacy, sustainability, and safety of VDZ therapy. As further information surfaces with VDZ and as the number of medical treatment options for moderate-severe CD and UC increases, studies should be evaluated in a context that enables choosing the most effective medication regimen at the appropriate disease timepoint in a particular patient. VARSITY, the first head-to-head trial comparing biologic treatments, found that in patients with moderately to severely active UC, VDZ was superior to adalimumab in achieving clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission [11]. Further comparative IBD drug studies can help clarify the impact of VDZ and other therapies in an increasingly crowded field of therapeutic options in order to guide practitioners to the optimal treatment strategy for each patient.

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