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In Case You Missed It

Vedolizumab Is Superior to Adalimumab for Clinical Remission and Endoscopic Improvement of Ulcerative Colitis: The VARSITY RCT

IBD

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This summary reviews Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med 2019;381(13):1215-26.

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STRUCTURED ABSTRACT

Question: Is there a difference in efficacy and safety between vedolizumab, an anti-integrin monoclonal antibody, and adalimumab, an anti-tumor necrosis factor (anti-TNF) monoclonal antibody for moderate-severe ulcerative colitis (UC)?

Design: Phase 3b randomized, double-blind, double-dummy, 52-week trial (VARSITY trial), the first randomized controlled trial (RCT) to directly compare 2 biologic agents for the treatment of UC.

Setting: The trial included 245 centers across 34 countries from July 2015 through January 2019.

Patients: Included 769 adults (383 vedolizumab, 386 adalimumab) with moderate-to-severe UC, based on Mayo score $\geq$ 6 (scale 0-12) and endoscopic subscore of 2-3 (scale 0-3).

Interventions: Vedolizumab 300 mg intravenous (IV) at week 0, 2, 6 and then every 8 weeks vs adalimumab 160 mg subcutaneous (subq) on week 0, 80mg subq on week 2, and 40mg subq every 2 weeks without dose optimization due to double -blind, double-dummy protocol.

Outcomes: The primary outcome was clinical remission at week 52, defined as Mayo score 0-2 with no subscore >1. Mayo score includes rectal bleeding score (0 -3), stool frequency score (0-3), centrally-assessed endoscopy subscore (0-3), and Physician's Global Assessment (0-3). Additional outcomes included endoscopic improvement (Mayo endoscopic subscore of ≤1), corticosteroid-free remission at week 52, and adverse events (including infections), among others.

Data Analysis: Modified intention-to-treat analysis defined as patients who were randomized and received at least 1 dose of study medication was performed for the primary endpoint with Cochran-Mantel-Haenszel chi-square test. A hierarchical closed-testing procedure was used for analysis of secondary endpoints to control the inflation of type I error rate for multiple efficacy outcomes.

Funding: Takeda Pharmaceuticals, manufacturer of vedolizumab.

Results: Patient characteristics included male: 56-61%, mean age: 41; White: 88-90%; duration of UC: 6-7 years; prior anti-TNF treatment: 19-21%; concurrent use of corticosteroids only: 36%; concurrent immunomodulators only: 26%. At week 52, significantly more patients in the vedolizumab group achieved clinical remission (31.3% vs 22.5%, P=0.006) and endoscopic improvement (39.7% vs 27.7%, P<0.001) compared to adalimumab. Corticosteroid-free remission was numerically lower in the vedolizumab group vs the adalimumab group (12.6% vs 21.8%), which was not statistically significant (P>0.05). Infections occurred less frequently in the vedolizumab group (23.4 vs 34.6 events per 100 patient-years). Selected outcomes are presented in **Figure 1.**

COMMENTARY

Why Is This Important?

With a growing number of available biologic therapies for UC, treatment decisions have become increasingly complex. In addition to anti-TNF agents (e.g. infliximab and adalimumab), vedolizumab, a gut-selective, anti-integrin monoclonal antibody, and ustekinumab, an anti-interleukin-12/23 monoclonal antibody, are available, as are small molecules like ozanimod, a sphingosine-1 phosphate inhibitor, and upadacitinib, a selective JAK1 inhibitor. Without head-to-head comparisons, positioning was based primarily on network meta-analyses of placebo-controlled trials as well as real-world data.[1,2] VARSITY was groundbreaking as the first RCT to directly compare the efficacy and safety of 2 biologic agents for the treatment of moderate-to-severe ulcerative colitis, demonstrating generally greater efficacy and fewer infections for vedolizumab versus

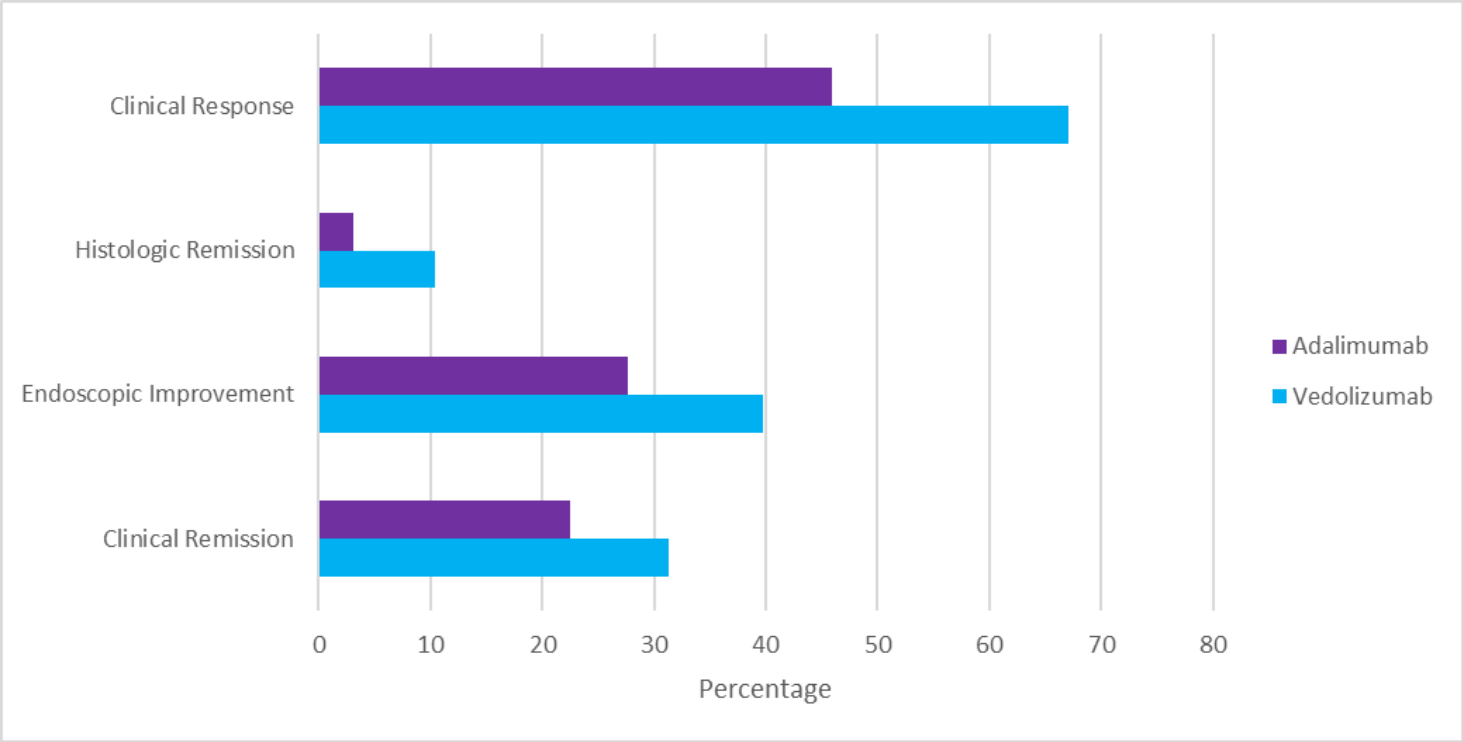

Figure 1. Selected outcomes of vedolizumab vs adalimumab for ulcerative colitis. Clinical response is at week 14 and clinical remission, endoscopic improvement, and histologic remission at week 52. vedolizumab statistically superior to adalimumab ($P< 0.05$) for all listed outcomes.

adalimumab.

Vedolizumab, which is only approved for treatment of UC and Crohn's disease, inhibits adhesion of gut-homing T lymphocytes to mucosal addressin-cell adhesion molecule 1, which should selectively down regulate gut inflammation while preserving systemic immune responses. Theoretically, this should make it particularly effective for gut inflammation while minimizing concurrent infections. This made it a particularly good comparator to the standard of care biologics, anti-TNF agents, when the VARSITY RCT was conducted.

Since VARSITY, a 2020 meta-analysis identified infliximab as the preferred first-line agent for ulcerative colitis, with ustekinumab and tofacitinib as preferred agents among those who were previously exposed to anti-TNF agents; vedolizumab had the lowest risk of infections.[3] Since the approval of upadacitinib, upadacitinib appears to be the most effective agent for the induction of clinical remission of ulcerative colitis, while vedolizumab still appears to be the safest according to a 2022 meta-analysis of clinical trials.[4] However, additional head-to-head comparisons are needed.

Key Study Findings

At week 52, significantly more patients in the vedolizumab group achieved clinical remission (31.3% vs 22.5%, P=0.006) and endoscopic improvement (39.7% vs 27.7%, P<0.001) compared to adalimumab, but not corticosteroid-free clinical remission, for patients in the vedolizumab group vs the adalimumab group. Fewer infections (23.4

vs 34.6 events per 100 patient-years) were also observed in the vedolizumab group.

Caution

It's unclear why corticosteroid-free remission was numerically higher with adalimumab while other outcomes demonstrated greater efficacy with vedolizumab over adalimumab. Due to the double-blinded and double-dummy trial design, dose optimization of either biologic was not possible. In real-world practice, dose optimization of either vedolizumab and adalimumab may positively influence clinical response. Therefore, these trial results may not reflect outcomes observed in clinical practice.

My Practice

Due to my own observations in clinical practice and the findings of VARSITY, I tend to favor vedolizumab over adalimumab as a first-line or later therapy for ulcerative colitis. However other considerations, such as patient preference regarding infusions and self-injections may factor into my decision. I may also consider adalimumab among individuals who had a robust response to infliximab, but developed anti-drug antibodies. These patients may benefit from a trial of another anti-TNF prior to switching out of class. The findings of VARSITY also do not affect my use of adalimumab for Crohn's disease, where it may be more effective.

For Future Research

Future research should prioritize head-to-head trials and real world studies directly comparing other biologics and small molecules for ulcerative colitis. Due to the challenges of comparing data from individual placebo-controlled trials, head-to-head comparisons are essential to guide biologic and small molecule positioning. Also, RCTs comparing dual biologic therapy in both UC and Crohn's disease are underway given the high rates of primary and secondary non-response among IBD patients.

Conflicts of Interest

Dr. Dalal has received grant support from Janssen Pharmaceuticals and Pfizer Pharmaceuticals and has served as a consultant for Centaur Labs. Dr. Allegretti has received grant support from Janssen Pharmaceuticals, Pfizer Pharmaceuticals, and Merck Pharmaceuticals, and has served as a consultant for Janssen Pharmaceuticals, Pfizer Pharmaceuticals, AbbVie Pharmaceuticals, Ferring Pharmaceuticals, Merck Pharmaceuticals, Bristol Myers Squibb, Seres Therapeutics, Finch Therapeutics, Iterative Scopes, and Takeda Pharmaceuticals.

Note: The authors of the article published in NEJM are active on social media. Tag the to discuss their work and this EBGI summary.

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