EVIDENCE-BASED GI
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The New Frontier of Combination Therapy for IBD: The VEGA RCT

Dr Tarun Chhibba
Guest Contributor

Dr Bharati Kochar
Associate Editor

Tarun Chhibba, MD[1] and Bharati Kochar, MD, MS[2]

[1]*Advanced Fellow in Inflammatory Bowel Diseases, Division of Gastroenterology, Massachusetts General Hospital, Harvard Medical School , Boston, MA*

[2]*Assistant Professor of Medicine, Division of Gastroenterology, Massachusetts General Hospital, Investigator, The Mongan Institute, Harvard Medical School, Boston, MA*

IBD

This summary reviews Feagan BG, Sands BE, Sandborn WJ, et al. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. Lancet Gastroenterol Hepatol 2023; 8: 307-20 .

Correspondence to Philip Schoenfeld, MD, MSEd, MSc. Editor-in-Chief. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Is combined treatment with guselkumab (Tremfya, Janssen Biotech, Horsham, PA), an IL-23 antagonist monoclonal antibody, and golimumab (Simponi, Janssen Biotech, Horsham, PA), a tumor necrosis factor (TNF)-antagonist monoclonal antibody, superior to golimumab or guselkumab alone for the treatment of moderate to severe ulcerative colitis?

Study Design: The VEGA study is Phase 2 proof of concept, randomized, double-blind, placebo-controlled trial (RCT) to compare 3 arms of therapy: (1) guselkumab and golimumab in combination (2) guselkumab monotherapy and (3) golimumab monotherapy.

Setting: Patients were recruited from 54 hospitals in 9 countries.

Patients: Study inclusion criteria included: age 18-65 years; confirmed diagnosis of ulcerative colitis 3 months prior to screening**;** moderate-to-severe disease activity defined by baseline Mayo score of 6-12 including an endoscopy subscore of ≥ 2; no prior treatment with anti-TNF, anti-interleukin (IL)12/23 or anti-IL23 agents; and inadequate response or failure to tolerate "conventional therapy" or corticosteroid dependence. Multiple exclusion criteria were used, including pregnancy; ulcerative proctitis only; history of colonic resection; or severe disease likely to lead to colectomy within 12 weeks.

Study enrollment mandated a 2-week washout period for immunomodulators (6-MP, azathioprine, methotrexate), rectal corticosteroids, rectal 5-aminosalicylic acid (ASA) compounds, total parenteral or enteral nutrition and antibiotics being used to treat ulcerative colitis (UC) and intravenous (IV) steroids. Patients treated with JAK inhibitors, cyclosporine or 6-thioguanine were required to have a 4-week washout period. Concomitant immunomodulator use was not permitted. Patients treated with vedolizumab were required to have an 18-week washout period. For 5-ASA, budesonide, and prednisone equivalents of <20mg daily, the dose must have been stable for at least 2 weeks prior to enrollment.

Intervention: Patients were assigned to 1 of 3 intervention arms: (a) Combination therapy: guselkumab 200mg IV at weeks 0, 4 and 8 followed by 100mg SC every 8 weeks until week 32 + golimumab 200mg SC at week 0, then golimumab 100mg SC at weeks 2, 6 and 10; (b) Guselkumab monotherapy: guselkumab 200mg IV at weeks 0, 4 and 8 followed by 100mg SC every 8 weeks until week 32; or, (c) Golimumab monotherapy: golimumab 200mg SC at week 0, then 100mg at week 2 and every 4 weeks until week 34. Placebo administrations were provided to maintain masking.

Outcomes: The primary outcome was clinical response at week 12, defined as 30% decrease in the baseline Mayo score including a minimum decrease of ≥3 points with a decrease in rectal bleeding score of ≥1 point or a rectal bleeding score of 0 or 1. The major secondary outcome was clinical remission at week 12, defined as Mayo score of ≤2 with no individual subscore of >1.

Other secondary endpoints at week 12 and 38 included: 7-day and 60-day corticosteroid-free clinical remission; symptomatic remission: stool frequency

subscore of 0 or 1 with no increase from baseline and rectal bleeding subscore of 0; endoscopic improvement: Mayo endoscopy subscore of 0 or 1 with no friability; histological remission at week 38; improvement in quality of life: inflammatory bowel disease (IBD) Questionnaire increase ≥ 16 points from baseline IBDQ score.

Analysis: The analysis was powered (80%) to detect a 20% difference in the primary outcome of clinical response at week 12. All randomly assigned patients who received 1 dose of study medication were included in the modified intention-to-treat analysis.

Funding: Janssen Research and Development funded this trial; Janssen, Inc is the manufacturer of both guselkumab and golimumab.

Results: Between 2018 and 2021, 358 patients were screened to identify 214 eligible patients: 48%-58% male, 92%-94% white, average disease duration of 5 years, and average Mayo score just under 9.

At week 12, there was a significantly greater clinical response in the combination compared to golimumab monotherapy arm (83% vs 61%, *P*=0.003), but no significant difference between the combination therapy and guselkumab therapy arm (83% vs 75%, *P*=0.216). For the major secondary outcome, clinical remission was more common in the combination therapy compared to guselkumab monotherapy arm (37% vs 21%, *P*=0.041) but not the golimumab monotherapy arm (37% vs 22%, *P*=0.058). The proportion of patients who achieved endoscopic improvement, endoscopic normalization and histologic remission were highest in the combination therapy arm compared to the monotherapy arms at weeks 12 and 38 (**Figure 1)**. Also notably, the proportion of patients who achieved a corticosteroid-free clinical remission at week 12 was significantly higher in the combination therapy arm than the monotherapy arms.

Incidence of serious adverse events were low: at week 12, 1% in the combination therapy arm, 1% in the golimumab monotherapy arm and 3% in the guselkumab monotherapy arm experienced a serious adverse event. In the combination therapy arm, this serious adverse event was a serious infection. No opportunistic infections occurred, and rates of infection (any type) was

12%-14% in all 3 arms. At week 50 follow up, there was 1 malignancy noted in the guselkumab monotherapy arm and 2 deaths, 1 in the combination therapy arm and 1 in the guselkumab monotherapy arm.

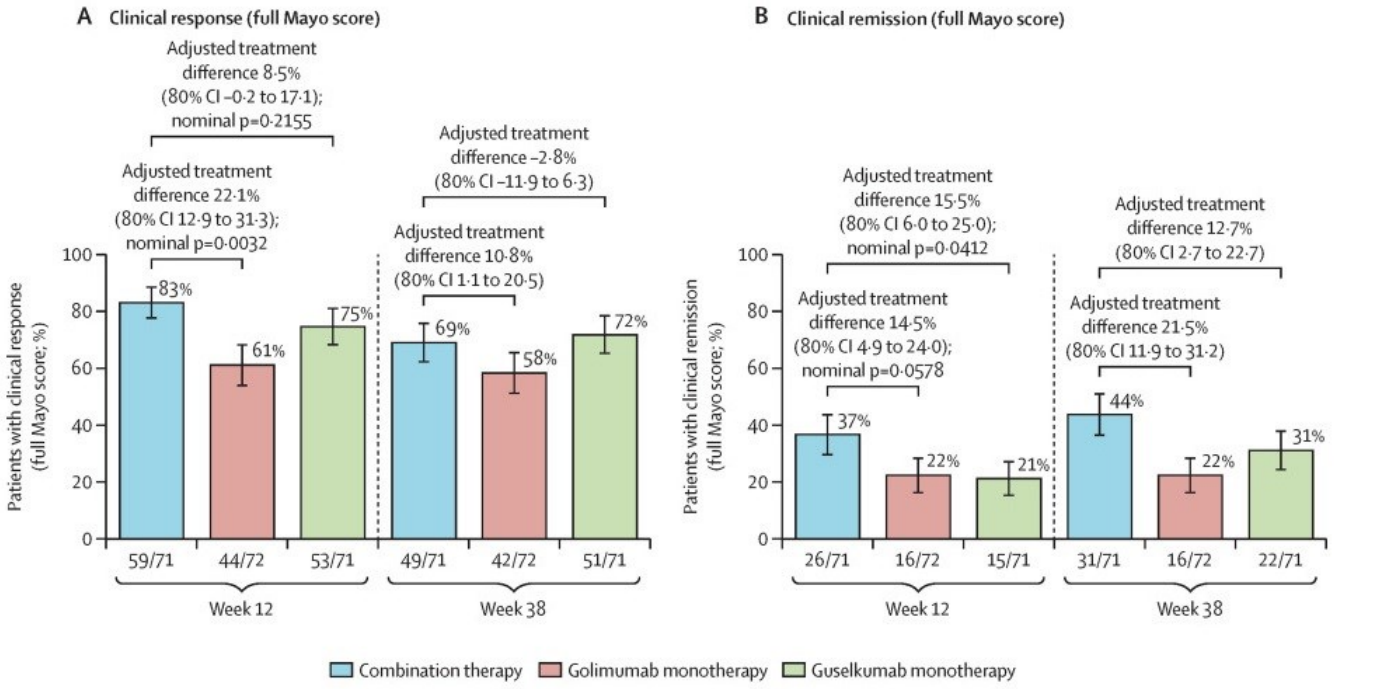

Figure 1. Clinical response and clinical remission at weeks 12 and 38 for golumumab monotherapy, guselkumab monotherapy, and combination therapy. Reprinted from *Lancet Gastroenterology Hepatology*, Feagan BG, Sands BE, Sandborn WJ et al. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. Pages 307-320. Copyright 2023, with permission from Elsevier.

COMMENTARY

Why Is This Important?

The publication of the SONIC[1] and U-SUCCESS[2] RCTs, which demonstrated the superiority of azathioprine plus infliximab over monotherapy for corticosteroid-free clinical remission in Crohn's and UC, revolutionized management of IBD. Multiple monoclonal antibodies with different mechanisms of actions are now available to treat UC, including vedolizumab, which is an anti-integrin antibody, anti-IL-12/23 monoclonal antibodies, like ustekinumab and risankizumab, as well as small molecules, like ozanimod, a sphingosine-1 phosphate inhibitor, and updacitinib, a selective JAK1 inhibitor. However, as monotherapy, these treatments produce clinical remission in only a minority of patients. Therefore, identifying optimal combination therapies that achieve higher remission rates *and* acceptable safety profiles is a huge knowledge gap in IBD management. While this proof of concept trial did not meet the primary outcome, it demonstrates that

prospective combination biologic agents can be safe and it's a critical step forward for the feasibility of these regimens.

Key Study Findings

In patients with moderate-severe UC who were naïve to biologic therapies, combination therapy with guselkumab and golimumab is safe and superior to golimumab monotherapy for clinical response at week 12 and just missed achieving statistical superiority compared to both monotherapies for clinical remission at week 12.

Other important secondary outcomes, such as endoscopic and histologic remission, were highest in the combination therapy arm of this relatively small trial.

Caution

The patient population was limited to patients that did not have prior treatment with anti-TNF agents or other biologic agents. Also, the sample size was relatively small and was underpowered to show differences <20% in clinical response rates.

My Practice

Combination biologics or combination biologic with JAK inhibitors is increasingly common in tertiary IBD practice. These should not be first or second line treatment strategies, but reserved for those with the most refractory disease. However, the VEGA trial asks an interesting question: should we be considering combination biologics as a strategy upfront? While the findings don't directly make the strongest argument for this, those in the combination arm, which only included combination therapy until week 10 with golimumab administration ending then, did have a numerically higher chance of experiencing clinical response and remission even as early as week 12. Perhaps more powerfully, this trial demonstrated that combination biologics are not unsafe.

Since guselkumab is not yet formally approved for the treatment of IBD, I am not using this in practice. However, I use golimumab in practice for patients who report a robust response to infliximab or adalimumab in the past, but are unable to restart the medication for a host of reasons. While golimumab is only formally FDA approved for the treatment of ulcerative colitis, when needed for refractory patients, I have requested approval to use it "off label" in patients with Crohn's disease as well.

My most commonly used combination advanced therapy for IBD is now vedolizumab in combination with a JAK inhibitor (JAKi). JAK inhibitors have potent inductive properties and the added benefit of not being immunogenic–meaning we can start and stop them as needed. Using this strategy over the span of a 1-2 years, I have even de-escalated patients to

vedolizumab monotherapy. Similarly, more recently, I have patients with whom I am treating with combination JAKi and anti-interleukin medications with the eventual goal of de-escalating to monotherapy with the anti-IL. Additionally, for those patients who have the most refractory disease that are either not good candidates for surgical management or decline surgical intervention, I am also turning to combination biologics – anti-TNFs with vedolizumab or anti-TNFs with anti-IL agents. This is in recognition of the fact that a multimodal approach is often needed to address severe disease. But it is always important to remind patients and include expert surgeons in the conversation because surgical management may need to be part of this multi-modal approach.

Whether it is for the treatment of IBD alone or the IBD with other medical conditions, including those that are not widely thought of as immune mediated inflammatory diseases, such as hypercholesterolemia or migraines, combination biologics is becoming a mainstay of treatment strategies. However, insurance companies pose great barriers to this strategy that incurs increased upfront investment. Trials like VEGA have the added benefit of providing the proof of concept needed to argue with insurance companies to approve appropriate care for patients.

For Future Research

VEGA joins an increasing cadre of active comparator clinical trials in IBD, which should be the norm, as placebo is no longer a viable comparator for medications. This trial sets the stage for understanding the clinical role of combination biologics. The mechanistic implications of combination biologics should be better elucidated. Furthermore, we need strategies beyond clinical acumen to identify which patient requires which medication or combination of medications.

Conflicts of Interest

Dr. Chhibba reports no conflicts of interests. Dr. Kochar reports serving as an advisory board member for Pfizer Pharmaceuticals.

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

@bruce_sands1

Bruce Sands

REFERENCES

1. Frederic-Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010; 362: 1383-95.
2. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology 2014; 146: 392-400.