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SEAVUE: A Sea of Change in Biologic Positioning for Crohn's Disease

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IBD

This summary reviews Sands BE, Irving PM, Hoops T, et al. Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial. Lancet 2022;399(10342):2200-2211.

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STRUCTURED ABSTRACT

Question: Is biologic monotherapy with ustekinumab, an anti-interleukin-12/23 monoclonal antibody, superior to adalimumab, an anti-tumor necrosis factor (anti-TNF) monoclonal antibody, for clinical remission in biologic-naïve patients with moderately to severely active Crohn's disease?

Design: The SEAVUE study is a 56-week, randomized, double-blind, double dummy, parallel-group, active comparator, phase 3b trial, the first randomized controlled trial (RCT) to directly compare 2 biologic agents for the treatment of Crohn's disease (CD).

Setting: Patients were recruited from 121 practices in 18 countries.

Patients: Inclusion criteria included: (a) age ≥18 years; (b) confirmed diagnosis of Crohn's disease; (c) no previous biologic therapy; (d) non-response or intolerance to "conventional therapy" OR corticosteroid dependence; (e) moderately to severely active disease, Crohn's disease activity index (CDAI) of

220-450, for at least 3 months; and, (f) at least 1 ulcer of any size on ileocolonoscopy (Simple Endoscopy Score for Crohn's Disease [SES-CD] ≥3). Exclusion criteria included, but were not limited to: (a) pregnancy; (b) abscess in prior 3-8 weeks; (c) bowel resection in prior 6 months; (d) ongoing infection or malignancy. [CDAI includes assessment of frequency of liquid stools, use of anti-diarrheals, severity of abdominal discomfort, general well-being, presence of extra-intestinal symptoms, hematocrit, weight loss, presence/absence of abdominal mass, anal fissure, fistulae, or fever.]

Prior to study enrollment, eligible patients completed a 3 week wash out period for thiopurines, methotrexate and intravenous (IV) corticosteroids and a 4 week wash out period for other immunosuppression such as Janus kinase inhibitors and cyclosporine. If patients were using oral corticosteroids, they required that the dose be stable and ≤40mg of prednisone-equivalents or ≤9mg of budesonide equivalents for at least 3 weeks prior to randomization.

Intervention: Ustekinumab 6mg/kg IV dose at day zero and then 90mg subcutaneous (subq) every 8 weeks through week 56 vs adalimumab 160 mg subq on day 0, 80mg subq on week 2, and 40mg subq every 2 weeks without dose optimization due to double-blind, double-dummy protocol and without additional use of immunomodulators.

Outcomes: The primary outcome was clinical remission at week 52, defined as CDAI score <150. Major secondary endpoints included: (a) corticosteroid-free remission: CDAI <150 + no corticosteroids at week 52; (b) clinical response: CDAI decrease at least 100 points from baseline at week 52; (c) PRO-2 symptom remission: mean daily abdominal pain score ≤1 with mean daily stool frequency score ≤3 at week 52; (d) clinical remission at week 16; and, (e) endoscopic remission, SES-CD ≤3 (or SES-CD 0 for patients who were 3 at baseline) at week 52. If study patients had Crohn's disease related surgery, treatment discontinuation due to an adverse event or prohibited change in concomitant medications during the 52 week study period, then this was also considered failure to achieve primary outcome of clinical remission.

Data Analysis: The analysis was powered (80%) to detect superiority of ustekinumab over adalimumab by 15% for the primary outcome of clinical remission at week 52. Sample size was calculated using data from Phase 3/3b studies for each group, assuming response rates of 56% and 41%, respectively, for ustekinumab and adalimumab. Modified intention-to-treat analysis defined as patients who were randomized and received at least one dose of study medication was performed for the primary endpoint with Cochran-Mantel-Haenszel chi-square test. Continuous

variables were assessed with analysis of covariance. A hierarchical testing procedure was used for analysis, starting with the primary endpoint to control the inflation of type I error rate for multiple efficacy outcomes. If the primary endpoint did not demonstrate a significant difference, then all major secondary outcomes were considered not statistically significant and p values were nominal.

Funding: Janssen Biotech, the manufacturer of ustekinumab, had a role in study design and employed study statisticians.

Results: Between June 2018 and December 2019, 633 patients were screened. Of the 386 patients who enrolled, 191 were randomly assigned to the ustekinumab arm and 195 to the adalimumab arm. Baseline characteristics were similar in both arms with a mean age of 37; 51%-53% female; 86%-93% White; mean disease duration of 5 years; and, mean CDAI score was 300-301. Over 50% of patients in both arms had ileocolonic involvement, 9%-16% had upper GI involvement and 9%-10% patients had fistulae. At baseline, 22%-24% of patients were treated with systemic corticosteroids.

There was no significant difference in clinical remission at week 52 between ustekinumab and adalimumab: 65% vs 61%, respectively, and no significant differences in the treatment arms for the major secondary endpoints (**Figure 1**), including endoscopic remission (29% vs 31%, respectively). Time to treatment discontinuation was significantly shorter in the adalimumab arm (P=0.047), and treatment discontinuation prior to week 52 was numerically higher with adalimumab (24% vs 15%).

Adverse event data reported infection with adalimumab (41%) and ustekinumab (34%), and serious infection occurred with adalimumab (3%) and ustekinumab (2%). Only abdominal pain (13% vs 8%) and headaches (12% vs 7%) occurred more frequently in the ustekinumab arm than in the adalimumab. Notably, they included a category of “Crohn’s disease events” which occurred more frequently in the adalimumab arm (16% vs 12%).

COMMENTARY

Why Is This Important?

Prior to SEAVUE and VARSITY, which is also reviewed in this issue, the comparative effectiveness and safety of biologics for inflammatory bowel disease (IBD) were primarily derived from large retrospective claims-based data, smaller retrospective electronic medical record-based data, or network meta-analyses of published studies. Such studies are valuable in the absence of prospective RCTs and more reflective of patients in practice. However, they are also inherently biased, most notably by confounding by

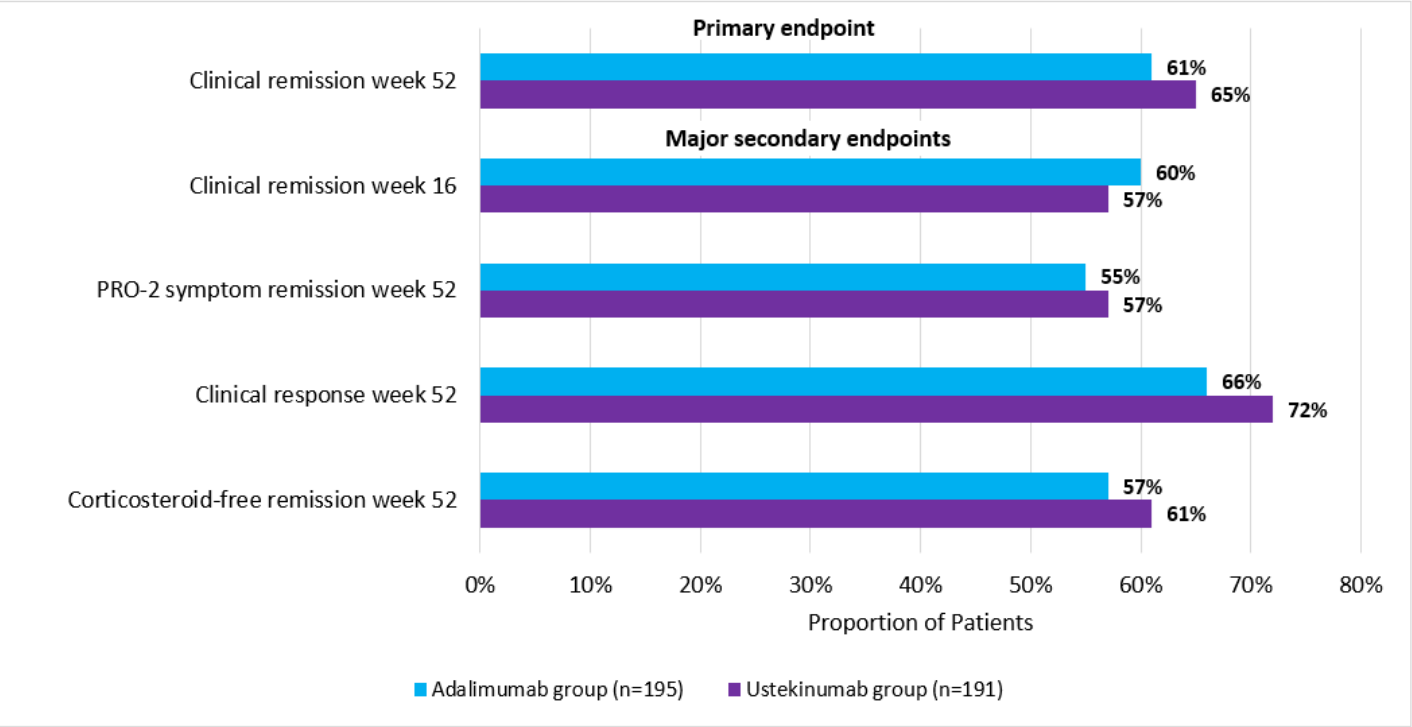

Figure 1. Primary and secondary study endpoints

indication which cannot be adequately adjusted for even by advanced statistical methodology.

SEAVUE is the first head-to-head RCT of biologic agents for the treatment of Crohn's disease, a seminal achievement. In the new therapeutic landscape of early biologic therapy and numerous treatment options for Crohn's disease, head-to-head trials more directly inform clinical care than the registration trials comparing a drug against placebo. When having a conversation with a patient about which medication to choose to treat their Crohn's disease in 2022, SEAVUE provides the most pertinent data to discuss. As with most rigorously -designed IBD clinical trials, many important details are limited to the appendix, although the manuscript itself is quite comprehensive. I encourage anyone treating patients with Crohn's disease to read the manuscript and appendices in their entirety.

Key Study Findings

In patients with moderate to severe Crohn's disease who have not been treated previously with a biologic agent, both ustekinumab and adalimumab have similar efficacy at achieving clinical remission at 52 weeks (65% vs 61%) without significant differences in clinical remission at 16 weeks, corticosteroid-free remission and improvement in patient-reported outcomes at 52 weeks.

Numerically, patients treated with ustekinumab had slightly lower rates of infections (34% vs 41%), serious infections (2% vs 3%), and Crohn's disease related adverse events (12% vs 16%) as well as longer time to treatment discontinuation.

Caution

Due to the double-blinded and double-dummy trial design, dose optimization of either biologic was not possible. Also, concurrent immunomodulator use (e.g., thiopurines) was not allowed. In real-world practice, dose optimization and immunomodulator use may positively influence clinical response. Since clinical remission rates are usually higher in biologically-naïve patients, these data may have limited generalizability to Crohn's disease patients who have tried and failed other biologic agents.

My Practice

The SEAVUE trial results had a pivotal impact on my clinical practice. Ustekinumab may confer an advantage related to treatment persistence and a numerically lower risk of infections, which is of great importance to patients, and I have been using these data in letters of medical necessity when requesting ustekinumab as a first-line biologic for the treatment of Crohn's disease. I do keep in mind that vedolizumab is also a great first line selective biologic agent for patients with colonic inflammation, whether it is Crohn's disease or ulcerative colitis.[1] While approximately 10% of the SEAVUE cohort did have fistulizing disease, I continue to prefer infliximab as first line therapy for penetrating Crohn's disease, as the ACCENT-II trial remains the largest dedicated trial of patients with fistulizing disease.[2] I also choose anti-TNF agents as first-line therapy if the patient has significant rheumatologic co-morbidities. For most other patients, especially for those with mild ileal Crohn's disease, anti-interleukin therapy with ustekinumab remains my preference for first-line therapy.

For Future Research

While SEAVUE and VARSITY helped us understand the most efficacious first line treatments, understanding the selection of the second biologic agent or identifying patients who benefit from combination biologic agents are other unmet needs. The ongoing VEGA trial, studying the combination of guselkumab with golimumab compared with guselkumab alone or golimumab alone, may shed some light on the role of combination biologics.[3] Despite the proliferation of treatments for IBD, durable response rates remain just above 50% and well under 90%, suggesting that we need to do better with selecting the right treatment for the patient. There is increasing work and investment in biomarker discovery for personalized therapy in IBD.

Conflicts of Interest

Dr. Kochar is an advisory board member for Pfizer Pharmaceuticals.

The authors of this article are active on social media. Tag them on Twitter to discuss this EBGI summary and other work:
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