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Etrasimod, a Sphingosine 1-Phosphate Receptor Modulator, for Moderate-Severe Ulcerative Colitis: New Options for Oral Therapy

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This summary reviews Sandborn WJ, Vermeire S, Peyrin-Biroulet L, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): Two randomised, double-blind, placebo-controlled, phase 3 studies. Lancet 2023; 401: 1159-71.

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STRUCTURED ABSTRACT

Question: Is etrasimod (Velsipity; Pfizer, Rochester, MI), a sphingosine 1-phosphate (S1P) receptor modulator, superior to placebo for clinical remission at week 12 and week 52 in moderately to severely active ulcerative colitis (UC)?

Design: To assess induction of remission at 12 weeks, 2 multi-center, double-blind, placebo-controlled randomly controlled trials (RCTs; ELEVATE UC 12 and ELEVATE UC 52) were conducted with 2:1 randomization assignment. In ELEVATE UC 52, patients completed an additional 40-week maintenance period using a treat-through design—patients were not re-randomized to etrasimod or placebo based on clinical response/remission after 12 weeks. Patients continued with their assigned treatment, etrasimod or placebo, for the entire 52 weeks. Randomization was stratified based on prior exposure to biologics or janus kinase (JAK) inhibitors, baseline corticosteroid use, and baseline disease severity.

Setting: In ELEVATE UC 12, 354 patients were enrolled between September 2020 and August 2021 at 407 sites across 37 countries. In ELEVATE UC 52, 433

patients were enrolled between June 2019 and January 2021 at 315 sites across 40 countries.

Patients: Inclusion criteria included: (a) 16-80 years old; (b) moderate-severe UC based on a modified Mayo Score of 4-9 with endoscopic subscore of $\geq$ 2, rectal bleeding subscore $\geq$ 1; (c) inadequate response, loss of response, or intolerance of at least 1 approved UC therapy. [Note: the modified Mayo Score assesses rectal bleeding score (0-3), stool frequency score (0-3), endoscopy subscore (0-3), so the score range is 0-9 with 9 representing most severe UC.] Patients with isolated proctitis (<10 cm of rectal involvement) who met other inclusion criteria were also enrolled. Patients on stable doses of 5-aminosalicylates (5-ASA), corticosteroids or budesonide were also allowed to enroll.

Exclusion criteria included clinically significant cardiovascular condition (e.g., myocardial infarction, stroke, second or third degree atrio-ventricular block), history of opportunistic infections or macular edema, pregnancy or lactation, and prior history of failing to induce remission with $\geq$ 3 biologic agents or JAK1 inhibitors.

Interventions/Exposure: Etrasimod 2mg oral daily vs placebo.

Outcome: Primary endpoint was clinical remission after 12 weeks, defined as: rectal-bleeding sub score 0; stool-frequency sub score $\leq$1 with a decrease of at least 1 from baseline; and, an endoscopy sub score $\leq$ 1. For ELEVATE UC 52, a co-primary endpoint was clinical remission at week 52. Multiple secondary endpoints were assessed, including: (a) symptomatic response; (b) endoscopic improvement, defined as endoscopy sub score $\leq$ 1 without friability; (c) endoscopic improvement plus histologic remission and, (c) clinical response.

Data Analysis: Modified intention-to-treat (ITT) analysis defined as patients who were randomized and received at least 1 dose of study medication was performed for the primary endpoint using the Cochran-Mantel-Haenszel method. Safety analysis performed for any patient who received study medication in both induction and maintenance RCTs.

Funding: Pfizer, manufacturer of etrasimod.

Results: Patient characteristics across both RCTs included mean age 39-41, mean disease duration 6-7 years, mean modified Mayo Score at baseline 6.6, prior biologic or JAK1 inhibitor therapy (37%-38%), concomitant steroid use at start of trial (32%-33%). Extent of colitis was: pancolitis (32%-35%), left-sided colitis (54%-63%), isolated proctitis (4%-10%). Etrasimod 2 mg oral daily was superior to placebo for producing clinical remission at week 12 (27% vs 7%, P <0.001 in ELEVATE UC 52 and 25% vs 17%, P = 0.026 in ELEVATE UC 12) and at week 52 (32% vs 7%, P <0.001 in ELEVATE UC 52).

Etrasimod 2mg oral daily was superior to placebo for key secondary endpoints at week 12 and week 52, including endoscopic improvement, symptomatic remission, and endoscopic improvement + histologic remission. For the prespecified secondary endpoint of clinical response at week 12, etrasimod was also superior in ELEVATE UC 52 (62% vs 34%, $P < 0.001$) and ELEVATE UC 12 (62% vs 41%, $P = 0.0002$).

Adverse events of special interest, including opportunistic infections, herpes zoster, and macular edema, were low (≤ 1%) and similar between groups. No malignancies were reported. Absolute lymphocyte count decreased by approximately 50% from baseline after 2 weeks in the etrasimod-treated patients. Among 527 etrasimod-treated patients, 9 bradycardia events were reported on days 1-2 with 2 being accompanied by mild-moderate dizziness, and 3 asymptomatic patients were identified with AV block, type 1 or 2.

***Note**: Although these trials used a classic double-blind, placebo-controlled, randomized study design with modified ITT analysis, study methodology and results are too detailed to summarize comprehensively. Readers are encouraged to review the full study publication.*

COMMENTARY

Why Is This Important?

As discussed in prior summaries[1], multiple UC treatments have become available in the past 5 years. In addition to commonly used anti-TNF antibody treatments like infliximab and adalimumab, anti-integrin antibody treatments like vedolizumab, anti-interleukin-12/23 antibodies such as ustekinumab and risankizumab, and JAK1 inhibitors like upadacitinib and tofacitinib are approved by the US Food and Drug Administration for use. Given this expanding menu of therapies, new algorithms are needed to help gastroenterologists choose preferred treatment for individual UC patients by accounting for the strengths and limitations of individual agents.[2]

Etrasimod is an oral sphingosine 1-phosphate (S1P) receptor modulator, which partially and reversibly blocks the trafficking of lymphocytes from lymphoid organs to the peripheral blood and appears to minimize lymphocyte mobilization to inflammatory sites. It's the second oral S1P receptor modulator to become available for treatment of UC after ozanimod (Zeposia; Bristol Myers Squibb, Princeton, NJ). Notably, a 7-day dose escalation is recommended with ozanimod to minimize bradycardia, while no dose escalation is recommended with etrasimod. The ELEVATE trials included isolated ulcerative proctitis patients, who are usually excluded from these types of studies and oral etrasimod may be an option if these patients fail to respond to oral and/or topical 5-ASA

treatment. As opposed to biologic agents, the risk of opportunistic infections may be lower with S1P receptor modulators based on mechanism of action, but comparative RCTs are lacking.

Also, since the prescribing information warns of the potential for cardiac arrythmias, opportunistic infections, liver injury and macular edema, patients should get complete blood count, electrocardiogram, liver function tests, and ophthalmic assessment before or near the start of treatment. In particular, the recommendation for ophthalmic assessment may delay initiation of treatment. Patients should get vaccination against varicella-zoster virus or demonstrate antibodies to the virus prior to initiating treatment.

Ultimately, Sandborn and colleagues should again be commended for designing a methodologically rigorous RCT. The use of the treat-thru approach in ELEVATE UC 52 is unique and may be particularly helpful since it more closely replicates clinical practice and provides estimates of delayed clinical response/ remission after 12 weeks.

Key Study Findings

Etrasimod 2 mg oral daily was superior to placebo for producing clinical remission at week 12 (27% vs 7% in ELEVATE UC 52 and 25% vs 17% in ELEVATE. UC 12) and at week 52 (32% vs 7% in ELEVATE UC 52).

Caution

A minority of study patients were previously treated with biologic agents, which may impact generalizability of results. Also, it's unclear why there were numerical differences in placebo rates of clinical remission between ELEVATE UC 52 and ELEVATE UC 12.

My Practice

Etrasimod may be ideal for UC patients with moderate disease activity who prefer an oral agent and who do not have a history of cardiovascular events as well as ulcerative proctitis patients resistant to standard oral therapies. We avoid it in patients that are pregnant or planning for pregnancy in the near future. If patients have severe snoring, which may represent undiagnosed sleep apnea, we may avoid it. Ultimately, we individualize our care by reviewing risks and benefits of different therapies with each patient and conduct shared decision making.

For Future Research

Future RCTs may define efficacy of etrasimod for Crohn's disease. Given the increasing number of available agents with different mechanisms of actions, comparative RCTs would be welcome to help establish positioning of therapies as well as longer-term safety data, including in pregnant women.

Conflict of Interest

Dr. Schoenfeld reports no conflicts of interest. Dr. Dalal has received grant

support from Janssen Pharmaceuticals and Pfizer Pharmaceuticals and has served as a consultant for Centaur Labs.

Note: The authors of ELEVATE UC 12 and ELEVATE UC 52 are active on social media. Tag them to discuss their work and this EBGI summary:

@bruce_sands1 (Bruce Sands)

REFERENCES

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