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The Edge of a New Frontier: Anti-TL1A Monoclonal Antibodies for Ulcerative Colitis

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IBD

This summary reviews Sands BE, Feagan BG, Biroulet LP, et al. Phase 2 trial of anti-TL1A monoclonal antibody tulisokibart for ulcerative colitis. N Engl J Med 2024; 391: 1119-29.

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STRUCTURED ABSTRACT

Question: What is the efficacy and safety of tulisokibart, a tumor necrosis factor–like cytokine 1A monoclonal antibody (anti-TL1A) in patients with moderate to severe active ulcerative colitis (UC)?

Design: A phase 2, multicenter, double-blind, placebo-controlled trial (ARTEMIS-UC trial).

Setting: The trial was conducted in 14 countries, with enrollment from North America, Western Europe, Eastern Europe, and Australia.

Patients: Adults diagnosed with moderately to severely active colitis (defined by modified Mayo score of 4-9, an endoscopic subscore of ≥2, and rectal-bleeding

subscore of ≥ 1) with glucocorticoid dependence or treatment failure or intolerance to one or more conventional or advanced therapies approved for the treatment of UC. Notable exclusion criteria included UC limited to < 15 cm from the anal verge, fulminant colitis, surgical resection within 3 months of screening, concomitant primary sclerosing cholangitis, unresected low grade or high-grade dysplasia, severe disease affecting other organs (kidneys, liver, blood, lungs, heart, neurologic, ophthalmologic or cerebral), history of cancer within 5 years, risk for tuberculosis reactivation, active infections, or bacterial infections within 3 months.

Interventions: The study was conducted in 2 cohorts. Cohort 1 was agnostic to testing for drug response. Cohort 2 was limited to people who had a genetic-based diagnostic test to identify people with an increased likelihood of response to the anti-TL1A antibody. In both cohorts, patients were randomly assigned in a 1:1 ratio to receive intravenous tulisokibart at a dose of 1,000 mg on day 1, followed by 500 mg at weeks 2, 6, and 10, or placebo at the same time points.

Outcomes: The primary efficacy end point was clinical remission at week 12 in cohort 1, defined as a modified Mayo endoscopic subscore of 0-1, a rectal-bleeding subscore of 0, and a stool-frequency subscore of 0-1 and not greater than the baseline value. Secondary end points assessed at week 12 were endoscopic improvement, clinical response, symptomatic remission, histologic improvement, histologic–endoscopic mucosal improvement, mucosal healing, and Inflammatory Bowel Disease Questionnaire (IBDQ) response. The partial Mayo score (comprising the stool-frequency subscore, rectal-bleeding subscore, and physician's global assessment subscore) was an exploratory end point; each subscore has a range of 0-3, with higher scores indicating greater severity. Antibodies to tulisokibart were measured with the use of a high-sensitivity, drug-tolerant assay. Inflammatory activity was assessed by high-sensitivity C-reactve protein (CRP) and fecal calprotectin. Safety was assessed through monitoring of adverse events, physical examination, measurement of vital signs, electrocardiography, and laboratory evaluations.

Data analysis: The primary analysis, performed in cohort 1, assessed clinical remission at week 12. In addition, patients with a positive test for likelihood of response from cohorts 1 and 2 were combined in prespecified sub-group analyses to assess the efficacy of tulisokibart.

The efficacy analysis followed a modified intention-to-treat principle, including all randomized patients who received at least 1 dose of tulisokibart or placebo. The

primary endpoint was tested between trial groups at a 2-sided significance level of 0.05 using the Cochran–Mantel–Haenszel test, with stratification by prior advanced therapy exposure and status of the test for likelihood of response. Treatment difference was estimated. Changes in IBDQ scores, fecal calprotectin, and CRP were summarized with descriptive statistics.

Funding: The trial was funded by Prometheus Biosciences, a subsidiary of Merck, the manufacturer of tulisokibart.

Results: Patients in all trial arms had similar baseline characteristics. Among 135 patients randomized in cohort 1 and 75 patients randomized in cohort 2, mean age varied from 37-42 years old, mean duration of disease, 6-8 years, mean modified Mayo score 7, and 48%-53% had prior biologic therapy. In cohort 1, a significantly higher percentage of patients receiving tulisokibart achieved clinical remission vs placebo at 12 weeks: 26% vs 1%, respectively; difference, 25 percentage points; 95% confidence interval [CI], 14 to 37; $P < 0.001$ (**Figure 1**). Additionally, tulisokibart-treated patients were more likely than placebo-treated patients to achieve endoscopic improvement, clinical response, and other secondary endpoints (Figure 1), as well as greater decreases CRP, fecal calprotectin, and change from baseline in the total IBDQ score. Subgroup analyses for clinical remission and endoscopic improvement showed a consistent benefit of tulisokibart as compared with placebo in patients receiving concurrent glucocorticoids and immunosuppressants.

A supplemental analysis combined patients with a positive test for likelihood of response from cohorts 1 (n=32) and cohort 2 (n = 43). In this patient group, tulisokibart-treated patients were more likely to achieve clinical remission at week 12 vs placebo-treated patients: 32% vs 11%, respectively; difference, 21 percentage points; 95% CI, 2 to 38; $P = 0.02$). However, tulisokibart-treated patients in this combined cohort trended toward endoscopic improvement vs placebo-treated patients, but did not quite attain statistical significance: 37% vs 19%, respectively; difference, 18 percentage points; 95% CI: -2 to 36; $P = 0.06$.

Among all the enrolled patients (cohorts 1 and 2), the percentage of patients reporting an adverse event was similar in the 2 trial groups (46% in the tulisokibart group and 43% in the placebo group). Most adverse events were mild to moderate in severity. Infections were the most common adverse event with 18% in both the drug arm and placebo arm experiencing an infection. Worsening UC was also assessed as an adverse event and occurred in 10% of patients in the placebo arm and 1% of patients in the drug arm.

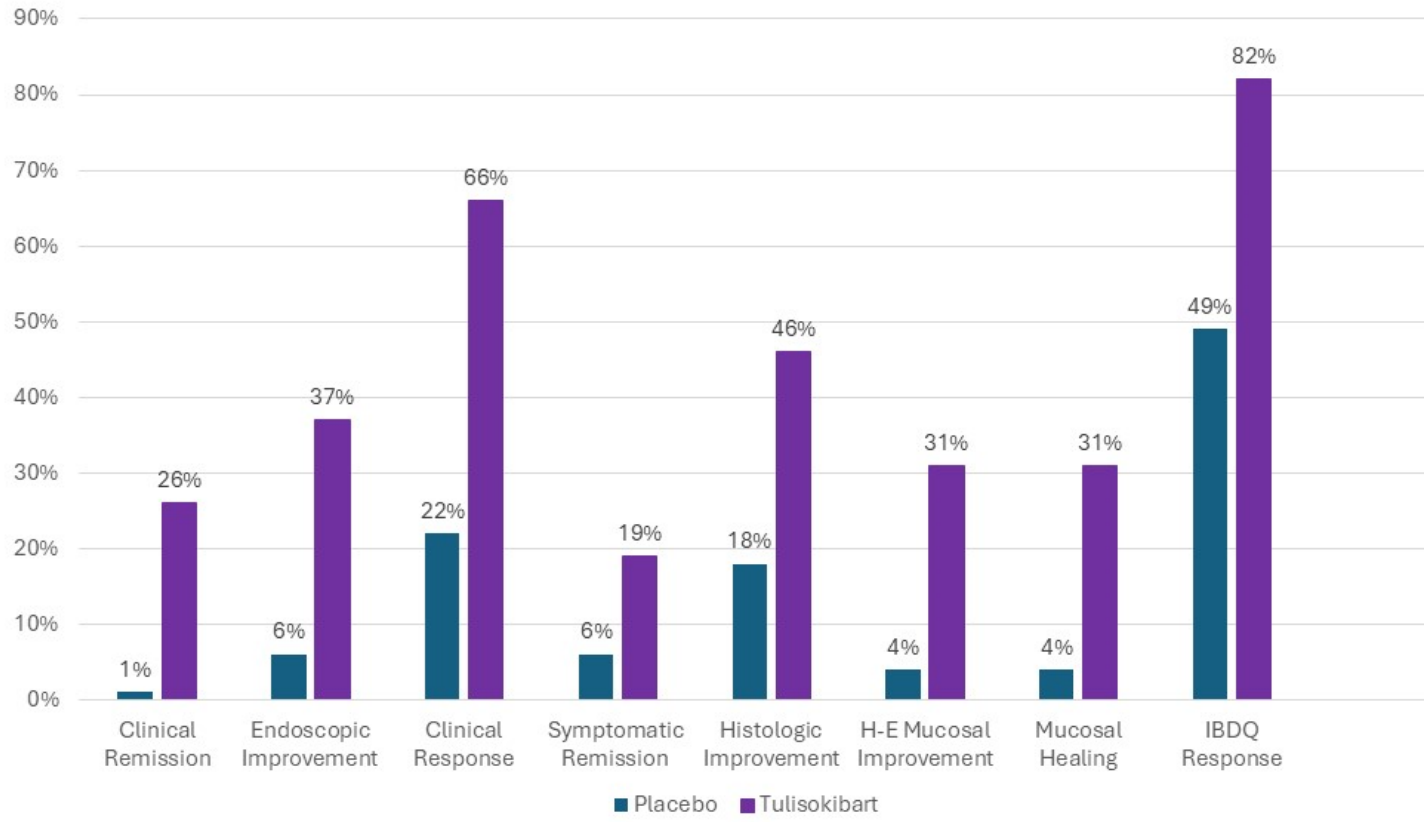

Figure 1. Percentage of patients reaching primary and secondary endpoint results in Cohort 1 (n=135). Primary endpoint was clinical remission. H-E, histologic-endoscopic.

COMMENTARY

Why Is This Study Important?

The therapeutic armamentarium for the treatment of moderate-to-severe UC has expanded rapidly over the past decade. However, it has been 5 years since the approval of a new biologic mechanism for the treatment of ulcerative colitis: Ustekinumab, an IL-23 targeted monoclonal antibody introduced in 2019. (Ozanimod, an oral sphingosine-1-phosphate modulator/small molecule was approved in 2021.) Therefore, tulisokibart offers the potential for a new treatment for UC patients that failed other biologic agents. It's a humanized IgG1-kappa monoclonal antibody that binds to TL1A with high affinity and specificity, preventing the interaction of TL1A and DR3. This suppresses type 1 and type 17 helper T-cell responses, enhances regulatory T-cell activity, and reduces pro-fibrotic pathways.[1] Ultimately, there are 2 exciting possibilities with this class of agents based on prior research. First, it may disrupt the fibrostenotic process that occurs as part of the inflammatory cascade in IBD patients. Second, genetic polymorphisms may identify patients that are more and less likely to respond to anti-TL1A monoclonal antibodies. Thus, there is the potential to provide IBD patients with precision-medicine approach

where treatment is selected based on a predictive biomarker.

While the proportion of patients who met the primary end point (clinical remission) in this trial is low (26%), that only 1% of patients in the placebo arm met this end point suggests that this was a highly treatment refractory population with nearly half the patients in the trial not demonstrating sustained response to an advanced therapy.[2] This is much more reflective of real-life practice. Also, higher proportions of patients demonstrated clinical response (66% vs 22%) and improvement in quality of life (82% vs 49%). These are promising numbers especially given that the endpoints were only assessed at 12 weeks.

Another novel aspect of this trial is the use of a genetic-based diagnostic test to predict response to the drug and stratify cohorts based upon this. While the test itself was only discussed briefly in the main article, data from the appendix reveals that a PCR-based assay was developed by the study sponsor which then evaluated polymorphisms in the genotypes related to TL1A biology. Testing was conducted by buccal swabs, and a machine-learning based approach to identify genotypes associated with therapeutic response was utilized. While this test has not been studied for clinical use and is not commercially available, this test and future iterations of the biomarker test represent hope for being able to better tailor medications to our patients.

Key Study Findings

Tulisokibart, a monoclonal antibody directed against TL1A, was more effective than placebo for induction of clinical remission at week 12 in patients with moderately to severely active ulcerative colitis.

Adverse events were similar in both drug and placebo arms: the overall adverse event rate was 46% in the drug arm and 43% in the placebo arm, however, only 1% of were serious adverse events in the drug arm and 8% in the placebo arm. Tulisokibart is a promising drug to study in a large Phase III clinical trial setting for the treatment of moderate to severe ulcerative colitis, even in those patients who have not been able to tolerate or have not had adequate response to other advanced therapies.

Caution

This study is only a Phase 2 trial, with a small number of people (90 in the drug arm and 88 in the placebo arm). Furthermore, the published data are only for induction and assess outcomes at 12 weeks, whereas the more meaningful outcomes are longer term. Phase 3 trials with larger cohorts and a longer duration to assess the impact of maintenance therapy is necessary to confirm the efficacy and safety of tulisokibart for treating moderate to severe ulcerative colitis. Additionally, the analysis of patients with a positive test for likelihood of response was constrained by a small sam-

ple size, as these patients were pooled from cohorts 1 and 2. Dedicated studies of the predictive value of this proprietary diagnostic assay are needed.

My Practice

Presently, this trial has not changed my clinical practice. However, it does offer hope for patients who have only had a good response to anti-TNF agents, without a response to small molecules or other biologic mechanisms. The recently published living UC guidelines and accompanying evidence synthesis highlight that while there are multiple approved highly efficacious treatments for UC for advanced therapy naïve patients: anti-TNF monoclonal antibodies, anti-integrin monoclonal antibodies, anti-IL 23 monoclonal antibodies, sphingosine-1-phosphate modulators, and JAK1 inhibitors. However, only JAK1 inhibitors and ustekinumab, an anti-IL23 monoclonal antibody are recommended for UC patients that previously tried and failed other advanced therapies.[3, 4] Unfortunately, ustekinumab tends to be a slower acting medication. Therefore, if tulisokibart continues to perform well in Phase 3 trials, then it may be a preferred biologic agent for advanced therapy experienced patients in light of the early response seen in this induction trial, at least for patients where JAK1 inhibitors are contraindicated.

Ultimately, it takes many years to bring a drug to the market, so it is not yet time to start speaking to our patients about this novel mechanism being a therapeutic option. Nevertheless, it's quite exciting to have a potentially new biologic agent with a unique mechanism of action which also has the potential to use a biomarker to identify patients most likely to be responders.

For Future Research

A Phase 2 trial to test the efficacy of tulisokibart for the treatment of Crohn's disease has been completed as well and both the UC and CD programs have moved to Phase 3 trials, which is promising. This drug is also being studied in much earlier stages for systemic sclerosis associated interstitial lung disease. It's possible that understanding the response to the anti-TL1A pathway in immune-mediated inflammatory disorders can help disentangle the complex relationship between inflammation and fibrosis. Additionally, this trial was novel in using a diagnostic test to predict response and not having chronologic age limits for exclusion. However, it is time to move beyond the placebo controlled new drug trial, which in this therapeutic era, I would argue is not just impractical from a recruitment standpoint, but also unethical.

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