EVIDENCE-BASED GI
AN ACG PUBLICATION

Tulisokibart: A New Drug for Moderate-to-Severe UC That May Come With Personalized Medicine

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IBD

This summary reviews Sands BE, Feagan BG, Peyrin-Biroulet L, et al and the ARTEMIS-UC Study Group. Phase 2 trial of anti-TL1A monoclonal antibody tulisokibart for ulcerative colitis. N Engl J Med. 2024;391(12):1119-1129 .

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Keywords: Ulcerative colitis, tulisokibart, RCT, IBD

STRUCTURED ABSTRACT

Questions: Among patients with moderate to severe ulcerative colitis (UC), is induction therapy with tulisokibart more effective than placebo? Is there a benefit to genetic-based testing for likelihood of response?

Design: Phase 2, multicenter, double blind, placebo-controlled trial with 12 weeks of follow-up. Eligible patients were enrolled in cohort 1 regardless of their status on a genetic-based diagnostic test. Enrollment in cohort 2 was limited to patients with a positive test for likelihood of response.

Setting: This trial was conducted in 14 countries.

Patients: Patients included in the study were adult patients with a diagnosis of moderately to severely active disease extending at least 15 cm from the anal verge. Moderately to severely active disease was defined by a 3-component modified Mayo score. Patients were eligible if they had glucocorticoid dependence. Patients were excluded if prior failure of more than 3 classes or more than 4 advanced therapies approved for UC.

Interventions: Participants received 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, defined as a modified Mayo endoscopic subscore of 0 or 1, a rectal-bleeding subscore of 0, and a stool-frequency subscore of 0 or 1 and not greater than the baseline value. Prespecified secondary end points that were assessed at week 12 were endoscopic improvement, clinical response, symptomatic remission, histologic improvement, histologic-endoscopic mucosal improvement, mucosal healing, and Inflammatory Bowel Disease Questionnaire response improvement.

Data Analysis: Analysis was based on the modified intention-to-treat principle, with the inclusion of all randomly assigned patients (for cohort 1) who had received at least 1 dose of tulisokibart or placebo. Analyses of the primary and secondary end points were prespecified and were conducted with the use of a sequential hierarchical testing procedure to control for multiple comparisons with a familywise alpha level (2-sided) of 0.05.

Funding: This study was supported by Prometheus Biosciences, a subsidiary of Merck.

Results: A total of 135 out of 198 screened patients were randomized. The baseline characteristics of the patients indicated a relatively refractory population with moderately to severely active ulcerative colitis. About half of the patients had prior exposure to advanced therapies. The trial sample was broadly representative of the demographic characteristics of individuals with ulcerative colitis in the countries where the patients were enrolled.

In cohort 1, 135 patients were randomized. A significantly higher proportion of pa-

tients who received tulisokibart achieved clinical remission compared to those who received placebo (26% vs 1%; 95% CI, 14 to 37; P <0.001). Tulisokibart also demonstrated significant benefits over placebo across all ranked secondary endpoints.

In the group of 75 patients with a positive likelihood of response test, a higher percentage of those who received tulisokibart achieved clinical remission at week 12 compared to those who received placebo (32% vs 11%; 95% CI, 2 to 38; P=0.02).

The incidence of adverse events was similar between the two groups, with 46% of patients in the tulisokibart group and 43% in the placebo group reporting adverse events.

	Tulisokibart (N= 68)	Placebo (N=67)	Δ
Clinical remission	**26%**	**1%**	**25%**
Endoscopic improvement	37%	6%	31%
Clinical response	66%	22%	44%
Symptomatic remission	19%	6%	13%
Histologic improvement	46%	18%	29%
Histologic-endoscopic musical improvement	31%	4%	27%
Mucosal healing	31%	4%	27%
IBDQ response	82%	49%	33%

Table 1. Outcomes at week 12.

IBDQ, inflammatory bowel disease questionnaire.

COMMENTARY

Why Is This Important

Despite the explosion of new medications and mechanisms in recent years in the field of inflammatory bowel disease (IBD), disease remission remains far from a universal experience for patients living with IBD. Most of our medical therapies only achieve a clinical remission rate of approximately 40% at week 52.[1] This underscores the importance of continued advancement in therapeutic options to break through this "efficacy ceiling." There are several strategies working towards this goal, but this study highlights two important tactics: (1) a novel mechanism targeting a new molecule in the inflammatory pathway and (2) personalized medicine. This exploration of personalized medicine is what is particularly unique to this study. Although this was a negative study in the clinical utility of a genetic-based

diagnostic test which was designed to identify patients with an increased likelihood of response, this is a concept that will almost certainly become a common theme in future research in IBD therapeutics.

Key Study Findings

At week 12, a significantly higher percentage of patients in cohort 1 who received tulisokibart had clinical remission than those who received placebo. A significant benefit of tulisokibart as compared with placebo was also observed for all ranked secondary end points for cohort 1.

Subgroup analyses for clinical remission and endoscopic improvement showed a consistent benefit of tulisokibart as compared with placebo in prespecified subgroups, including patients receiving concurrent glucocorticoids and immunosuppressants

A greater percentage of patients with a positive test for the likelihood of response who received tulisokibart had clinical remission at week 12 than those who received placebo. The between-group difference for endoscopic improvement in patients with a positive test for likelihood of response was not significant. Among all the enrolled patients for both cohorts, the percentage of patients reporting an adverse event was similar in the 2 trial groups (46% and 43% in the tulisokibart and placebo groups, respectively).

Caution

As a phase 2 trial, this study is inherently limited in the inability adequately evaluate the therapeutic index or the positioning of tulisokibart in the IBD medications armamentarium. Future assessment of larger numbers in a phase 3 trial with longer-term follow will provide more precise efficacy and safety evaluations. The analysis of patients with a positive test for likelihood of response was based on pooled patients from cohorts 1 and 2 and is therefore limited by the small sample size and may be susceptible to selection bias due to cohort differences. Additionally, caution should be exercised when analyzing cohort 2 which selected for patients with a positive test for likelihood of response, and has therefore lost randomization.

My Practice

At our institution, we are enrolling patients in the phase 3 study for tulisokibart. The typical patient that is enrolled is a relatively refractory phenotype that, from a clinical perspective, closely reflects that of the population studied in the phase 2 trial. Patients are often considered for enrollment with moderate to severe disease, higher Mayo endoscopic subscores, and most importantly prior failure several lines of therapy. At this point it is unclear where tulisokibart would fit into the treatment algorithm compared to other biologics/small molecules for the treatment of ulcerative colitis based on this study. It should also be noted that our practice is guided by treat-to-target

guidelines outlined by STRIDE II that support the use of endoscopic healing rather than this study's primary outcome of clinical remission as the therapeutic target.[2]

For Future Research

The currently underway phase 3 trials of tulisokibart in treatment of moderate-to-severe UC will elucidate where this patient falls in the treatment algorithm for UC. With a larger patient population, it will be interesting to see if there is benefit to using the genetic-based diagnostic test. Beyond a larger cohort size to increase power of the study, the cohort used to evaluate the genetic-based testing for likelihood of response should be designed to maintain randomization for more accurate results.

Conflict of Interest

The authors report no potential conflicts of interest related to this study.

Abbreviations

CI, confidence interval; IBD, inflammatory bowel disease; UC, ulcerative colitis.

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