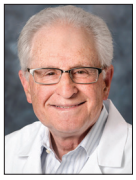
ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Exploring the Potential of TL1A Inhibition in the Treatment of Inflammatory Bowel Disease Patients



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G&H How does tumor necrosis factor-like ligand 1A differ from tumor necrosis factor?

ST In 2002, my colleagues at Cedars-Sinai and I discovered the expression of tumor necrosis factor-like ligand 1A (TL1A) on the surface of T cells. TL1A is quite different from tumor necrosis factor (TNF). TL1A has more downstream effects on the entire body. In particular, TL1A has a major role, both directly and indirectly, on scarring. In contrast, TNF itself does not regulate scarring; it just takes away inflammation. TL1A inhibition will likely play a role not just in inflammatory bowel disease (IBD) but in other types of immune-mediated diseases that involve scarring, such as systemic sclerosis and steatotic liver disease.

G&H What research has been conducted on TL1A inhibitors thus far for the treatment of patients with IBD?

ST Results have been published from 2 trials thus far on the anti-TL1A monoclonal antibody tulisokibart (originally generated at Cedars-Sinai and modified at Merck), and I have been involved with both. The first was a controlled trial in patients with moderately to severely active ulcerative colitis, the results of which were published in September 2024 in *The New England Journal of Medicine*. Tulisokibart directly modulates inflammation and indirectly modulates the body's anti-inflammatory mechanisms. This trial consisted of patients who had not only failed to respond to corticosteroids but also to 1, 2, or even 3 other biologics, including anti-TNF agents. Marked improvement was noted with the use of tulisokibart, which was given intravenously (1000 mg on day 1 and 500 mg at weeks 2, 6, and 10). The primary endpoint, clinical remission at week 12, was achieved in 26% of patients who received the drug compared with 1% of patients who received placebo. The researchers designed a genetic-based companion diagnostics test to help identify which patients were more likely to respond to the drug. Among patients who tested positive for the likelihood of response, a higher percentage of those in the tulisokibart arm (32%) achieved clinical remission than in the placebo arm (11%).

Results were recently published in *The Lancet Gastroenterology & Hepatology* on the use of tulisokibart in patients with Crohn's disease. Although this was not a placebo-controlled trial, this study showed promising results in the percentage of patients who responded to both the primary and secondary endpoints. These involved safety and the proportion of patients who

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experienced endoscopic response at week 12 (defined as a decrease in Simple Endoscopy Score for Crohn's Disease of at least 50% from baseline). Endoscopic response at week 12 was seen in 26% of patients receiving the drug. Adverse events were reported in 78% of patients, but most were mild to moderate in severity. These findings showed that tulisokibart may potentially be efficacious and well tolerated in patients with Crohn's disease, but researchers noted the need for confirmation with longer, randomized controlled trials.

Additionally, the anti-TL1A antibody afimkibart showed promise in a phase 2b trial of patients with ulcerative colitis, the results of which were recently published in *The Lancet Gastroenterology & Hepatology*. Although differences in the primary endpoint of clinical remission (total Mayo score) were not significant, secondary endpoints suggested that the drug had a favorable benefit-risk profile and clinically meaningful improvements in clinical remission in terms of the modified Mayo score, warranting further research.

G&H Where do you think TL1A inhibition will ultimately be positioned in the therapeutic realm for IBD?

ST I believe we are entering the era of precision medicine in IBD. Crohn's disease is not a single entity, and ulcerative colitis is not a single entity either. There are subtypes within each of these, as well as subtypes in the overlaps, and each of these has different pathways involved in their particular subtype of disease. I think TL1A will be the first target and molecule in which there will be companion diagnostics, like in oncology, where providers can predict which drug to use to obtain the best outcome in a particular patient. This is where treatment is going, and it is going to be accompanied by functional genomics. One of my colleagues was the first to describe the variation in the *TNSF15* gene that makes the TL1A protein. That haplotype is associated with both Crohn's disease and ulcerative colitis. Functional genomics says that people who express that haplotype express increased amounts of this protein over time, and this will play a dominant role in the inflammation seen in these patients. My colleagues and I created an animal model that did not knock out the protein but expressed it more. We were able to completely reproduce all aspects of Crohn's disease in a mouse, which had not been done before.

G&H Who would be the ideal patient to recommend for TL1A inhibition?

ST Essentially, the key in taking care of patients is durability. The phase 2 trials I mentioned previously lasted 3 months and showed positive results for patients who tested positive for the companion diagnostic. There are two phase 3 trials going on now. The companion diagnostic is being broadened in these phase 3 trials, which will last nearly a year. If the companion diagnostic pans out in phase 3 research, the ideal patients for this approach would be those who test positive for the diagnostic.

Having a companion diagnostic might help providers identify the right patients so that this approach can be used for first-line treatment, as opposed to third- or fourth-line treatment down the line.

It should be noted that there are often difficulties with coverage from payers and the need to fail to respond to other drugs first. Having a companion diagnostic might help providers identify the right patients so that this approach can be used for first-line treatment, as opposed to third- or fourth-line treatment down the line.

G&H Will patients with inadequate response to TNF inhibitors respond to TL1A inhibition?

ST Absolutely. In fact, the 2 trials showed that even patients with more-severe disease, who failed to respond not only to anti-TNF therapy but also to other therapies such as ustekinumab and up to 3 therapies in all, responded nicely to tulisokibart.

G&H What are the priorities of research in this area?

ST The priority in TL1A inhibition is to nail down the companion diagnostic. It was quite good in phase 2 but needs to be expanded to other diseases where there can be scarring, including extraintestinal manifestations of IBD and diseases with liver scarring. This approach is wide-open because it involves the first cytokine that not only blocks inflammation but, directly and indirectly, also blocks the laying down of collagen, which causes scarring, and can potentially even reverse it. In our animal

model, when my colleagues and I treated animals using TL1A inhibition after they developed inflammation, this approach reversed the inflammation as well as completely resolved the collagen deposition in the mucosa. This is the first approach that may be able to reverse early scarring and, if given early on, prevent it.

G&H Could you further discuss the studies currently ongoing in this area?

ST Because of the unique nature of TL1A inhibition, multiple companies are very interested in this approach. Both tulisokibart and afimkibart have completed phase 2 placebo-controlled trials in ulcerative colitis and Crohn's disease and are very far along in enrolling patients for phase 3 trials to see the durability of the response associated with this approach and whether the companion diagnostic predicts which patients will have acute response as well as durable response. There are also phase 2 trials underway with other types of antibodies to this protein. This approach is new to many general gastroenterologists and even to IBD experts, but there is a lot of excitement. I think this is the beginning of a new era and the first of many molecules using genetic variations to separate subsets of Crohn's disease and subsets of ulcerative colitis.

Disclosures

Dr Targan is a member of the Cedars-Sinai/Merck Steering Committee.

Suggested Reading

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