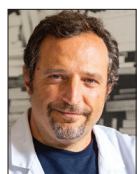


ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Combining Mechanisms of Action to Treat Patients With Inflammatory Bowel Disease



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G&H What is the rationale for combining mechanisms of action to treat patients with inflammatory bowel disease?

SD A therapeutic ceiling has been achieved in that most clinical trials of patients with inflammatory bowel disease (IBD) culminate in very similar rates of efficacy that are not very high. Typically, only approximately 30% of patients with IBD, possibly up to 40% in fortuitous circumstances, achieve clinical remission at the end of a trial, and those numbers have not been exceeded. One of the reasons may be that IBD requires multiple methods of shutting down inflammation because more than one inflammatory pathway is involved in the development and progression of the disease.

In addition, biopsies of patients with active IBD, regardless of whether it is ulcerative colitis or Crohn's disease, show increased tumor necrosis factor (TNF), interleukin (IL) 23, and cytokines. Historically, there were not many therapeutic options for patients with IBD, so only one treatment was used at a time. Intuitively, if pathogenesis of IBD involves overexpression of multiple cytokines, disease could be treated by blocking more than one cytokine at the same time. However, this remains to be proven.

G&H What was the biggest concern at first with trying different mechanisms of action to treat patients with IBD?

SD The biggest concern at first was safety because the IBD drugs available are generally immune suppressants. For example, there are safety concerns involving infection

when using a TNF blocker. What happens when 2 or 3 drugs with immunosuppressive properties are used? In addition, there are now drugs such as Janus kinase (JAK) inhibitors that are broad immune suppressants that block multiple cytokines at the same time. One of the key goals for treatment is achieving the best possible efficacy results without harming patients.

G&H What research is currently available on combining mechanisms of action in patients with IBD, and which combinations have been studied?

SD More than 20 case series and reports have been published. In addition, several retrospective studies have been conducted in different countries, including the United States, Italy, and Finland, that have varied in size and in the combinations used. (Possible combinations for patients with IBD are shown in the Table.) In several studies, the most common combination was vedolizumab (Entyvio, Takeda) plus ustekinumab (Stelara, Janssen) or an anti-TNF agent plus vedolizumab or ustekinumab. These studies have generally noted improved outcomes in patients taking combination therapy. There is also evidence that combining tofacitinib (Xeljanz, Pfizer) with a biologic (eg, vedolizumab or ustekinumab) can induce clinical and endoscopic improvements but no new safety signals.

Results from the first well-conducted clinical study on IBD combinations with different mechanisms of action were presented at the most recent European Crohn's and Colitis Organisation meeting and United European Gastroenterology Week. The VEGA study examined patients

Table. Possible Combinations in Inflammatory Bowel Disease

	Anti-TNF Agent	Vedolizumab	Ustekinumab	Anti-IL-23 Agent	JAK Inhibitor
Anti-TNF Agent	—	Yes	Yes	Yes	Too little evidence
Vedolizumab	Yes	—	Yes	Yes	Yes
Ustekinumab	Yes	Yes	—	Very similar MOA	Yes
Anti-IL-23 Agent	Yes	Yes	Very similar MOA	—	Too little evidence
JAK Inhibitor	Too little evidence	Yes	Too little evidence	Too little evidence	—

IL, interleukin; JAK, Janus kinase; MOA, mechanism of action; TNF, tumor necrosis factor.

Adapted from Danese S, Solitano V, Jairath V, Peyrin-Biroulet L. The future of drug development for inflammatory bowel disease: the need to ACT (advanced combination treatment). *Gut*. 2022;71(12):2380-2387.

with moderate to severe ulcerative colitis who were naive to biologic treatment, which is a key aspect. This study sought to evaluate whether combination therapy with the anti-TNF agent golimumab (Simponi, Janssen) and the IL-23 inhibitor guselkumab (Tremfya, Janssen) or monotherapy with either agent was better. Researchers found that more patients receiving combination therapy experienced clinical response than those receiving either agent

Rather than safety issues, the real concern of these combinations is the cost of using more than 1 therapy.

alone. Importantly, for the first time, efficacy was twice as high with this combination therapy for objective measures of disease control such as endoscopic improvement and histologic remission, not only for induction but also for maintenance. These are seminal data because they show that high efficacy rates can be achieved by combining 2 advanced agents with different mechanisms of action to treat patients with IBD.

It should be kept in mind that these study findings do not indicate that TNF inhibitors and IL-23 blockers are the best therapeutic combination for patients with IBD. Nevertheless, this is the first clinical trial evidence of a combination with different mechanisms of action changing disease management with a good safety profile. As previously noted, one of the key concerns for these combinations is safety. In this study, no safety issues were

reported for combination therapy, which reflects real-world experiences.

G&H Could you discuss any other safety data for combining mechanisms of action to treat patients with IBD?

SD I and several other IBD specialists recently published a large review in *Gut* that summarized all of the available evidence, and no major safety events were reported. This evidence included a recent systematic review and meta-analysis that showed that adverse event, infection, and malignancy rates were similar between patients taking combination therapy and those taking anti-TNF therapy alone.

Rather than safety issues, the real concern of these combinations is the cost of using more than 1 therapy. One of the main challenges that physicians and payers will face is determining who will pay for combination therapy.

G&H In which patients with IBD might combination therapy with different mechanisms of action be most useful?

SD The case series and retrospective studies published thus far have shown that these combinations are mainly being used in the most refractory patients in whom new treatment is being initiated, patients at high risk of developing complications, and patients with extraintestinal manifestations or immune-mediated diseases. The VEGA study also showed that combination therapy in patients naive to biologics is a better strategy than monotherapy to achieve better disease control and then maintain it.

I do not think that combinations theoretically need to be avoided in any particular patients who have IBD

unless the patients have contraindications to any of the treatments.

G&H Is any guidance available for using such combinations in clinical practice?

SD In our article in *Gut*, my colleagues and I noted that these combinations are currently considered experimental and off-label. However, we also pointed out that the combinations may be considered in a few specific scenarios—in patients who have IBD that is refractory, patients with an elevated risk of complications, and patients who have concomitant immune-mediated disease in whom the risk of uncontrolled disease outweighs the risk of using an additional therapy. Such treatment should be administered in centers with clinical expertise that provide multidisciplinary care. Agents with favorable safety profiles should be preferred (eg, vedolizumab and ustekinumab), particularly in patients who are frail or elderly. The patient's IBD phenotype should be considered when selecting agents. Anti-TNF agents should be preferred in Crohn's disease, and vedolizumab in ulcerative colitis. In patients who also have extraintestinal manifestations or immune-mediated disease, anti-TNF therapy, ustekinumab, or a JAK inhibitor is preferred. Anti-TNF treatment is also preferred in patients with Crohn's disease who have bowel damage.

G&H What studies are currently underway on different IBD combinations?

SD There are many ongoing combination treatment studies at this time. The VEGA study is still underway. Another ongoing study is EXPLORER (ClinicalTrials.gov identifier: NCT02764762), which is an open-label, uncontrolled study examining triple combination therapy consisting of vedolizumab, adalimumab, and oral methotrexate for the induction of endoscopic remission in selected patients with Crohn's disease. The future is very bright. We are awaiting larger studies to see if they

corroborate promising findings. If these combinations prove to be successful, they will have a large impact on IBD management.

Disclosures

Dr Danese has served as a speaker, consultant, and advisory board member for Schering-Plough, AbbVie, Actelion, Alphawasserman, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring, Genentech, Grunenthal, Johnson & Johnson, Millennium Takeda, MSD, Nikkiso Europe, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, UCB Pharma, and Vifor.

Suggested Reading

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