Two new studies evaluate agents for treating ulcerative colitis

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In the first clinical trial to evaluate two biologic therapies for moderate to severe ulcerative colitis (UC) head to head, Mount Sinai researchers found vedolizumab to be superior to adalimumab in a variety of measures. In a separate study, the investigators reported that ustekinumab is more effective than placebo as an induction and

maintenance therapy for UC. The studies were published today in the The *New England Journal of Medicine*.

Ulcerative colitis is one of many immune-mediated diseases with a rising prevalence worldwide. While there is no cure, available treatments include several classes of drugs, depending on the severity of the disease. All three biologic agents evaluated in these studies—adalimumab, vedolizumab, and ustekinumab—work through different mechanisms to modify the immune responses that causes bowel inflammation in ulcerative colitis. "Every patient responds differently to these agents, and the treatments we have today are not effective for everyone, adding to the urgency to identify treatments that are both safe and effective," says the Principal Investigator for both studies, Bruce E. Sands, MD, MS, Dr. Burrill B. Crohn Professor of Medicine (Gastroenterology) at the Icahn School of Medicine at Mount Sinai and Chief of Gastroenterology for the Mount Sinai Health System.

Vedolizumab versus adalimumab for moderate to severe ulcerative colitis

While newer classes of biologic agents have been approved to treat ulcerative colitis over the last 15 years, no study has yet directly evaluated and compared two biologic agents for inflammatory bowel disease in a blinded, randomized controlled trial. In a study of vedolizumab versus adalimumab, the VARSITY trial found vedolizumab to be superior to adalimumab in achieving clinical remission and endoscopic improvement at 52 weeks. No significant difference was found between the two agents in achieving corticosteroid-free remission. Both agents showed good safety over the year of treatment.

The VARSITY trial enrolled 769 patients with moderately to severely active UC across 244 centers in 34 countries in a phase 3b, randomized,

double-blind, double-dummy, active controlled study. Vedolizumab, versus adalimumab, achieved significantly higher week-52 rates of remission, 31.3 percent versus 22.5 percent, respectively, and endoscopic improvement of 39.7 percent versus 27.7 percent. Corticosteroid-free clinical remission rates were 12.6 percent for vedolizumab versus 21.8 percent for adalimumab, a difference that is not statistically significant. The authors note that adjusted adverse event rates were lower with vedolizumab, at 23.4 percent versus 34.6 percent per 100 patient years for infections, and for serious infections, the comparison is 1.6 versus 2.2. The study was funded by Takeda.

"The VARSITY study provides the highest level of evidence to date to guide the initial choice of biologic therapy in patients with moderately to severely active ulcerative colitis. Further head-to-head studies like VARSITY are needed to advance the field," says Dr. Sands.

Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis

In a study of ustekinumab as induction and maintenance therapy, investigators conclude that this agent is more effective than placebo for inducing and maintaining remission in patients with moderate to severe UC. Ustekinumab, already approved for the treatment of Crohn's disease, psoriatic arthritis, and psoriasis, blocks interleukin-12 and interleukin-23, immune proteins known to be involved in immune responses in inflammatory bowel disease and other immune-mediated conditions.

In the study, 961 patients were randomized to intravenous induction doses of ustekinumab or placebo. Clinical remission rates at week eight among patients receiving intravenous ustekinumab were significantly higher than placebo-treated patients. Rates of clinical remission among

patients who received intravenous ustekinumab, either 130 mg or approximately 6 mg/kg, were significantly higher than among those who received placebo, at 15.6 and 15.5 percent 151.5% vs. 5.3%; statistically significant for both comparisons. Among ustekinumab-treated induction responders, the rate of clinical remission at week 44 was significantly higher for patients re-randomized to subcutaneous ustekinumab than for patients re-randomized to placebo: 38.4 percent for patients dosed every 8 weeks and 43.8 percent for patients dosed every 12 weeks, versus 24 percent for those patients taking placebo injections. The authors note that serious adverse event rates were similar in ustekinumab- and placebo-treated patients. The study was funded by Janssen Research & Development, LLC.

"Given the excellent efficacy and safety of ustekinumab, this should be a valuable addition to the drugs we use to treat ulcerative colitis," says Dr. Sands.

More information: Bruce E. Sands et al. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis, *New England Journal of Medicine* (2019). DOI: 10.1056/NEJMoa1905725

Bruce E. Sands et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis, *New England Journal of Medicine* (2019). DOI: 10.1056/NEJMoa1900750

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