Editorial Commentary

Therapeutic updates for moderate to severe ulcerative colitis

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Ulcerative colitis is a chronic gastrointestinal illness characterized by episodic abdominal pain and diarrhea, often with the presence of blood. Patients generally require lifelong therapy in order to mitigate these debilitating symptoms and prevent complications and other poor outcomes. Goals of therapy include eliminating symptoms, improving quality of life, decreasing corticosteroid use, preventing hospitalizations, avoiding colectomy, and preventing colorectal dysplasia and subsequent cancer. While colectomy is curative and many experiences improved quality of life after surgery, patients must either have a permanent ileostomy or undergo an additional surgery for the creation of an ileoanal pouch anastomosis (1). The latter is most desired, particularly by younger patients, but it does not restore normal bowel function.

The mainstays of ulcerative colitis treatment prior to the biologic era consisted of oral and rectal aminosalicylate products (for example, mesalamine and sulfasalazine), corticosteroids, and thiopurines. Unfortunately, aminosalicylate products were often not sufficient for the treatment of moderate to severe ulcerative colitis, chronic corticosteroid use carries significant long-term adverse event risks including but not limited to osteoporosis, cardiovascular disease, hyperglycemia, and diabetes, as well as weight gain, and thiopurines are only effective in about one fourth of patients (2).

The development of novel intravenous and subcutaneous biologic medications targeting various steps in the inflammatory cascade have led to significant improvements in the management of ulcerative colitis including a decrease in colectomy rates over time (3). However, despite all of the current available therapies, not every patient is able to achieve induction of remission or maintenance of remission. Induction of remission rates for the anti-tumor necrosis factor (anti-TNF) agents infliximab or adalimumab were estimated at 33% (range, 27.5–38.8%) (4); likewise, maintenance of remission rates were estimated at 33% (range, 25.6–36.9%). Newer biologics such as vedolizumab and small molecules like tofacitinib have increased the armamentarium for patients with moderate to severe disease. However, rates of induction of remission and maintenance of remission for vedolizumab are also less than 40% (5), with similar rates for tofacitinib (6). Thus, new therapies for ulcerative colitis are still needed.

Until recently ustekinumab was only approved for use in Crohn's disease, psoriasis, and psoriatic arthritis. Ustekinumab is an antagonist of the p40 subunit of interleukin-12 and interleukin-23, proinflammatory cytokines implicated in the pathogenesis of inflammatory bowel disease. The Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Patients with Moderately to Severely Active Ulcerative Colitis (UNIFI) studied ustekinumab in 961 patients with moderate to severe ulcerative colitis (7), defined as a total Mayo score of 6–12 with at least a subscore of 2 on the endoscopic component. Of note, these patients had previously failed or not tolerated therapy with anti-TNF agents, vedolizumab, or other nonbiologic therapies.

Patients were randomized to an eight-week induction trial followed by a 44-week maintenance trial. The primary

endpoint of the induction trial was clinical remission, which was defined as a total Mayo score of ≤2 with no subscore >1. The primary endpoint of the maintenance trial was clinical remission at week 44, with major secondary endpoints including maintenance of clinical response through week 44 and corticosteroid-free clinical remission at week 44. Patients were randomly assigned to receive either 130 mg of IV ustekinumab, 6 mg/kg of IV ustekinumab, or placebo. Patients who responded clinically to ustekinumab entered the maintenance trial. Those who did not respond to placebo received a dose of ustekinumab; if they responded, they then also entered the maintenance trial. Patients in the maintenance trial were randomly assigned to receive 90 mg of subcutaneous ustekinumab every 12 weeks, 90 mg of subcutaneous ustekinumab every 8 weeks, or placebo. Throughout the trial, clinical symptoms were monitored as well as serum ustekinumab levels, anti-drug antibodies, serum and stool inflammatory markers, and histologic samples from endoscopic biopsies.

In the induction trial, the authors found a statistically significant difference in remission rates between patients who received ustekinumab and those who had received placebo with rates of 15.6% in the 130 mg group and 15.5% in the 6 mg/kg group compared with 5.3% in the placebo group (P<0.001 for both comparisons). Response and remission rates were lower in bio-exposed compared to bio-naïve patients. Additionally, among those patients who demonstrated a response in the induction trial and were randomized into the maintenance trial, there was a statistically significant increase in rates of clinical remission among those patients who received ustekinumab compared to those who received placebo, with rates of 38.4% in the every 12 weeks group, 43.8% in the every 8 weeks group, and 24.0% in the placebo group (P=0.002 for comparison between 12 week group and placebo group, P<0.001 for comparison between 8 week group and placebo group).

The results of UNIFI led to the Food and Drug Association approval of ustekinumab in patients with moderate to severe ulcerative colitis (8), thereby increasing the arsenal of medications for use in this condition.

Precision medicine is currently lacking in the management of ulcerative colitis. The American Gastroenterological Association has recognized risk factors associated with a greater risk of colectomy in patients with ulcerative colitis that can guide clinicians to use of early highly effective biologic or small molecule therapy (9). Nevertheless, while a clinician may decide that biologic or small molecule therapy is appropriate in a patient with moderate to severe symptoms and/or risk factors for colectomy, which medication to choose first, and which to subsequently try after initial treatment failure, are decisions based on provider and patient preference as opposed to head-to-head trials. Furthermore, diagnostic tests are not available to risk-stratify patients or to predict response to medical treatment. This knowledge gap is troublesome to providers as a clear first, second, and even third choice for treatment is lacking in the literature and guidelines; unfortunately, payers and pharmacy benefit managers often decide which drug patients can receive.

The results of the Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis (VARSITY) trial were published in September 2019 (10). This was the first trial comparing two biologic medications head-to-head for use in ulcerative colitis. The study was sponsored by Takeda, the manufacturer of vedolizumab. The VARSITY trial was a phase 3 superiority trial comparing vedolizumab with adalimumab over 52 weeks. Vedolizumab is a monoclonal antibody targeting the integrin α4β7 subunit which prevents leukocyte trafficking to the intestinal tract. Adalimumab is an anti-TNF agent. The study population included patients with moderate to severe active ulcerative colitis, defined as a total Mayo score of 6–12 with at least 2 on the endoscopic subscore component. Eligible patients had never taken either medication in the past, but up to 25% of patients had taken other anti-TNF agents.

The primary outcome was clinical remission at week 52. The two secondary outcomes were improvement in the Mayo endoscopic subscore and corticosteroid-free clinical remission at week 52. An additional endpoint was histologic remission which the authors defined as a Geboes score of <2.0 and Robarts Histopathology Index score <3.

Seven hundred sixty-nine patients were randomized to vedolizumab or adalimumab. Patients in the vedolizumab arm received 300 mg IV vedolizumab at weeks 0, 2, 6, then every 8 weeks for 52 weeks; they also received subcutaneous placebo injections. Patients in the adalimumab arm received adalimumab subcutaneously with 160 mg at week 0, 80 mg at week 2, 40 mg at week 4, then 40 mg every 2 weeks for 52 weeks; they also received intravenous placebo infusions. Dose escalation was not permitted in either arm and corticosteroid tapering was at the discretion of the investigator. Throughout the trial, regular visits were scheduled with clinical assessment, stool inflammatory markers, and endoscopy at weeks 14 and 52.

A statistically higher proportion of patients in the vedolizumab group were in clinical remission at 52 weeks compared to adalimumab-treated patients (31.3%, versus

22.5%; P=0.006). Endoscopic improvement was also significantly higher in the vedolizumab compared to adalimumab group (39.7%, versus 27.7%; P<0.001). The rate of histologic remission was higher in the vedolizumab compared to adalimumab group (10.4%, versus 3.1% in the adalimumab group). However, the percentage of patients achieving corticosteroid-free remission was higher in the adalimumab compared to vedolizumab group (21.8%, versus 12.6%). In subgroup analyses, there was no significant difference in outcomes between vedolizumab and adalimumab in bio-exposed patients.

Both studies are groundbreaking and should have an immediate impact on clinical care. First, despite increasing treatment options for patients with ulcerative colitis, a significant proportion of patients do not respond or lose response to treatment. Thus, having another therapeutic option like ustekinumab is important. Additionally, ustekinumab represents a safe and convenient treatment option as it does not appear to increase the risk of infection, malignancy or paradoxical autoimmune reactions (11) and is given every 8 weeks via subcutaneous injection for maintenance treatment. The VARSITY trial is the first head-to-head trial of biologic therapies for ulcerative colitis and demonstrated superiority of vedolizumab to adalimumab (albeit in only one controlled trial). Providers may choose vedolizumab over adalimumab based on superior safety and now better efficacy. However, providers do not have information on how vedolizumab compares to infliximab or ustekinumab, patients may still prefer subcutaneous treatment, and payers may still restrict use of vedolizumab despite the results of the VARSITY trial. Future research is needed to develop biomarkers predicting severe disease and response to treatment. Furthermore, additional head-to-head trials (and some head-to-head-to-head) are ongoing comparing therapies in both ulcerative colitis and Crohn's disease.

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Footnote

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