EDITORIALS

Biologics beyond Anti-TNF Agents for Ulcerative Colitis — Efficacy, Safety, and Cost?

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Ulcerative colitis typically manifests in young adults in their 20s and 30s and can progress from mild asymptomatic rectal inflammation to debilitating extensive colitis resulting in frequent bloody stools, systemic symptoms, and colorectal cancer.[1] Approximately one third of patients with distal ulcerative colitis at the time of diagnosis will have more extensive colitis by 10 years,[2] and 10 to 15% of patients with ulcerative colitis will ultimately require a colectomy.[3-5]

Biologic agents are recommended for patients with moderate-to-severe ulcerative colitis who have not had a response to conventional therapies such as aminosalicylates, corticosteroids, or immunomodulators or who cannot receive such therapies because of unacceptable side effects.[6] The introduction of anti–tumor necrosis factor (TNF) biologics (e.g., infliximab, adalimumab, and golimumab) has revolutionized the management of ulcerative colitis in the past two decades and shifted the treatment goals from symptom control and clinical remission to achieving sustained corticosteroid-free remission.[7] However, 50% of patients with ulcerative colitis do not have a response to anti-TNF therapies or lose response over time, such that after 1 year of treatment, clinical remission is observed in only 17 to 34% of patients. Furthermore, the considerable risk of infection (with immunosuppressants in general and anti-TNF agents in particular) is an important concern, as are autoimmune and malignant complications.[8] Despite an improving treatment landscape, long-term rates of colectomy for ulcerative colitis have not declined over a 10-year period,[3] a fact that highlights the need for new biologic therapies and strategies.

Vedolizumab, a humanized immunoglobulin G_1 monoclonal antibody against the $\alpha_4\beta_7$ integrin that inhibits adhesion of gut-homing T lymphocytes to mucosal addressin-cell adhesion molecule 1, selectively down-regulates gut inflammation while preserving systemic immune responses. The efficacy and safety of induction and maintenance therapy with vedolizumab was shown in the GEMINI 1 trial involving patients with moderate-to-severe ulcerative colitis.[9] Ustekinumab, a monoclonal antibody against the p40 subunit of interleukin-12 and interleukin-23, has been approved for the treatment of psoriasis and psoriatic arthritis and more recently, after the UNITI trials, for Crohn's disease.[10]

In this issue of the *Journal*, Sands et al. report the results of two large trials of biologics in patients with moderate-to-severe ulcerative colitis, a considerable proportion of whom had no response to other biologics. The VARSITY trial, a double-blind, double-dummy, randomized, controlled trial, compared intravenous infusions of vedolizumab with subcutaneous injections of adalimumab,[11] and the UNIFI trial reports the results of a single intravenous infusion of ustekinumab followed by subcutaneous maintenance injections.[12]

The results from the VARSITY trial showed that clinical remission at week 52 occurred in a significantly higher percentage of patients who received vedolizumab than in those who received adalimumab (31.3% vs. 22.5%), as did endoscopic improvement (39.7% vs. 27.7%); the treatment effects were most pronounced in patients who had not previously received anti-TNF therapies. There were more adverse events, especially infections, among the patients in the adalimu-

mab group than among those in the vedolizumab group. However, the percentage of patients who had corticosteroid-free clinical remission at week 52 (a key secondary end point) was higher in the adalimumab group than in the vedolizumab group (21.8% vs. 12.6%). In the VARSITY trial, which was funded by the manufacturer of vedolizumab (Takeda), the fact that previous exposure to anti-TNF therapies was allowed (albeit restricted to 25% of the patients), as well as the lack of dose escalation in either treatment group (dose escalation is more typically performed with adalimumab than with vedolizumab in clinical practice), may have skewed the results in favor of vedolizumab.

The results from the UNIFI trial showed that clinical remission at week 8 occurred in a significantly higher percentage of patients who received a single infusion of ustekinumab, at both doses studied (130 mg and 6 mg per kg of body weight), than in those who received placebo (15.6% and 15.5% vs. 5.3%, respectively). Among the patients who had had a response to induction treatment with ustekinumab and underwent a second randomization, clinical remission at week 44 occurred in a significantly higher percentage of those who received 90 mg of subcutaneous ustekinumab every 12 weeks or every 8 weeks than among those who received placebo (38.4% and 43.8% vs. 24.0%, respectively). Clinical response, endoscopic healing, corticosteroid-free clinical remission, and health-related quality-of-life scores were significantly better in the two ustekinumab groups than in the placebo group. One or multiple biologics, including anti-TNF agents or vedolizumab or both, had previously failed in at least 50% of the trial participants, and although a significant benefit was observed among the patients who had not previously received biologics (a finding similar to that in the VARSITY trial), a significant benefit was also observed among the patients in whom therapy with a biologic had previously failed.

Although the VARSITY trial presents a head-to-head comparison of biologics for inflammatory bowel disease and aims to determine the first-line biologic therapy for ulcerative colitis, any clinical superiority of vedolizumab should be balanced against the significant cost advantages of a subcutaneous regimen of adalimumab. In many respects, the ideal trial to assess whether vedolizumab should supplant anti-TNF therapies would involve a head-to-head comparison of infliximab infusions with vedolizumab infusions in patients who have not previously received anti-TNF therapies. The UNIFI trial assessed the combination of a single induction infusion followed by a maintenance subcutaneous regimen in patients with ulcerative colitis and may lead to the assessment of similar regimens in future trials of biologics in an effort to reduce our dependence on expensive, completely infusion-based biologic regimens, not to mention to relieve pressure on our increasingly busy infusion units. Indeed, the landscape of biologic therapies for ulcerative colitis has changed so dramatically over the past decade with the widespread introduction of less-expensive infliximab and adalimumab biosimilars, as well as vedolizumab, oral Janus kinase inhibitors (tofacitinib),[13] and now ustekinumab, that biologics rather than hospitalization or colectomy are now the main driver of health care costs in the management of inflammatory bowel disease.[14]

The findings in both these trials by Sands et al. highlight the importance of alternative biologic treatments and regimens for ulcerative colitis in patients who are not able to receive anti-TNF therapies because of unacceptable side effects or who have disease that is refractory to anti-TNF therapies. The cost-effectiveness of all biologics will have to come into sharper focus in future trials and longitudinal studies of biologics to help determine not only their eventual place in the treatment algorithm for moderate-to-severe ulcerative colitis but also the true effect of existing and newer biologics on disease course and rates of colectomy.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Emerging Use of CRISPR Technology — Chasing the Elusive HIV Cure

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A new form of gene therapy termed genetic editing or gene targeting has become possible owing to advances in genetic engineering technology.[1] The intent of genetic editing is to alter the DNA code in cells with single base-pair specificity, and thus it can be considered to be an ultimate form of precision therapy. For the past two decades, genome editing has been a powerful tool for basic science research. The importance of genome editing as a research tool was recognized in 2007 by the award of the Nobel Prize in Physiology or Medicine to Smithies, Capecchi, and Evans.

Until recently, the efficiency of genetic editing was insufficient to have therapeutic potential for clinical applications. However, the development of artificial nucleases (a nuclease is an enzyme that cleaves the base pairs in RNA or DNA) that cut DNA at a desired site has solved the problem of gene-targeting efficiency. These tools include homing endonucleases, zinc finger nucleases, transcription activator–like effector nucleases, and clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 9 (Cas9).[2] These platforms have all been tested in preclinical studies as tools to accomplish gene editing for the treatment of human immunodeficiency virus (HIV) infection (Fig. 1).

Antiretroviral therapy is highly effective in preventing HIV replication and transmission. The major barrier to achieving sustained treatment-free remissions is the existence of a long-lived HIV viral reservoir in patients receiving antiretroviral therapy. Two approaches are being pursued to achieve sustained remissions: eradication of the replication-competent HIV reservoir in CD4+ T cells; and control of HIV replication without eradication of HIV in the absence of treatment, which is referred to as sustained virologic remission. The primary strategies to eradicate the HIV reservoir currently involve gene editing and allogeneic stem-cell transplantation. The most advanced application of this approach is the generation of HIV resistance by genome editing the gene *CCR5*. Human genetics validates knocking out *CCR5* as a target because there are healthy persons with biallelic mutations in *CCR5* who consequently have resistance to HIV infection because the CCR5 protein is an essential coreceptor for most, but not all, forms of HIV infection. Two patients now appear to have had eradication of the HIV reservoir after stem-cell transplantation from a donor who was homozygous for the *CCR5*-Δ32 allele.[3,4]

In this issue of the *Journal*, Xu et al.[5] report the use of CRISPR–Cas9 gene editing in humans. The investigators selected an HLA-compatible