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MEETING THE NEEDS OF PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS

NOVEL TARGETS MEAN NEW OPPORTUNITIES

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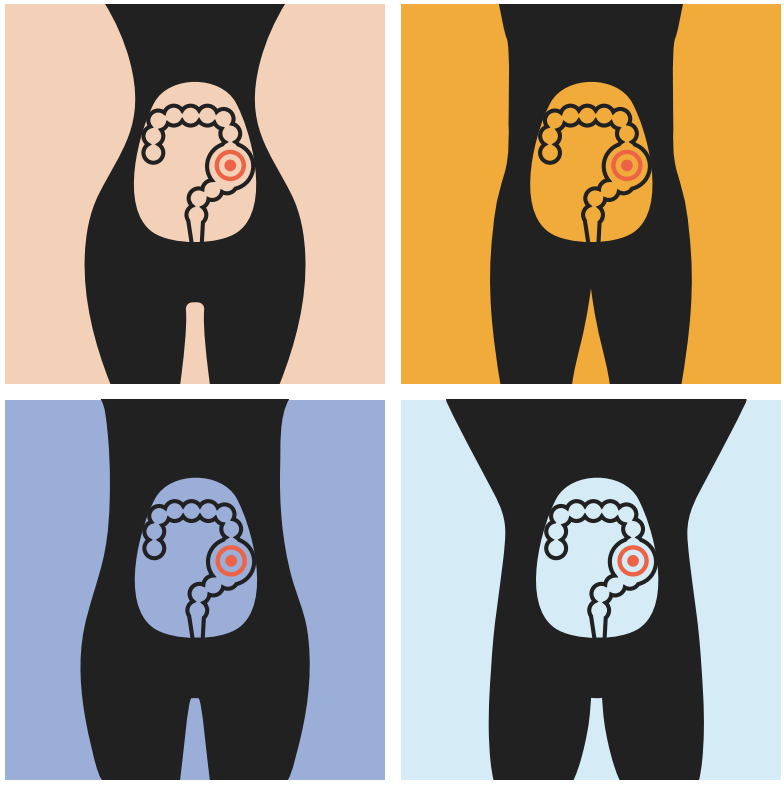

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FACULTY

William J. Sandborn, MD (Chair)
Marla C. Dubinsky, MD
David T. Rubin, MD

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Ulcerative colitis (UC) is a chronic inflammatory condition characterized by abdominal cramping, bloody stools, tenesmus, and urgency. Manifesting most often in adolescence and early adulthood, UC exhibits considerable clinical heterogeneity and frequently detracts from patient-related quality of life. Although the quantity and quality of options to treat UC has risen over time, opportunities remain to optimize care for those diagnosed with this highly disruptive disease. This educational activity summarizes strategies and considerations presented during a CME/CE symposium on May 21, 2021, during Digestive Disease Week 2021. The desired results of this educational activity are to improve the care of patients living with UC.

TARGET AUDIENCE

This educational activity is intended for gastroenterologists, gastroenterology physician assistants, and nurse practitioners involved in the care of patients with ulcerative colitis.

LEARNING OBJECTIVES

After completing this activity, participants will be better able to:

- Discuss the importance of considering the effect of ulcerative colitis on patients' quality of life
- Integrate disease activity and quality-of-life assessments into routine management of ulcerative colitis
- Describe the limitations associated with current treatments for moderate to severe ulcerative colitis
- Review current guidelines for treatment escalation as part of the management of moderate to severe ulcerative colitis
- Summarize recent clinical trials on emerging S1P treatments in ulcerative colitis
- Identify patients who would be good candidates for treatment with S1P modulators if and when they are approved

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MEETING THE NEEDS OF PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS

NOVEL TARGETS MEAN NEW OPPORTUNITIES

FACULTY

William J. Sandborn, MD
(Chair)
Distinguished Professor of Medicine
Division of Gastroenterology
University of California, San Diego
La Jolla, California

Marla C. Dubinsky, MD
Professor of Pediatrics and Medicine
Chief, Pediatric Gastroenterology and Nutrition
Mount Sinai Kravis Children's Hospital
Co-Director, Susan and Leonard Feinstein
Inflammatory Bowel Disease Clinical Center
Icahn School of Medicine at Mount Sinai
New York, New York

David T. Rubin, MD
Joseph B. Kirsner Professor of Medicine
Chief, Section of Gastroenterology,
Hepatology, and Nutrition
University of Chicago Medicine
Chicago, Illinois

INTRODUCTION

Ulcerative colitis (UC) is a chronic, inflammatory condition characterized by abdominal cramping, bloody stools, tenesmus, and urgency. Manifesting most often in adolescence and early adulthood, UC exhibits considerable clinical heterogeneity and frequently detracts from patient-related quality of life (QOL). Although the quantity and quality of options to treat UC have risen over time, opportunities remain to optimize care for those diagnosed with this highly disruptive disease. This educational activity summarizes strategies and considerations presented during a CME/CE symposium on May 21, 2021, during Digestive Disease Week 2021. The desired results of this educational activity are to improve the care of patients living with UC.

UNMET NEEDS IN ULCERATIVE COLITIS

Marla C. Dubinsky, MD

Improving Patient Communication and Assessing Effects on Quality of Life

Despite many advances in the treatment and management of UC, several unmet needs still exist. According to an expert panel of European gastroenterologists, patients with UC confront 4 distinct classes of unmet needs related to the disease's diagnosis, treatment, and effects on QOL[1]:

1. Ulcerative colitis impacts the ability to lead a normal life
2. Early diagnosis and treatment are important
3. Existing therapeutic options have significant drawbacks
4. New therapeutic options are needed

Additional research suggests the existence of substantial perception gaps between patients and caregivers in several key areas, most notably in assessments of disease burden, the definition of remission, and overarching goals of treatment.[2,3] These findings underscore the need for improved communication and better patient education, which in turn can promote greater treatment adherence and shared decision making.[4] Many opportunities exist to improve care of patients with UC, even as colectomy and hospitalization rates decline. To clarify treatment gaps and evaluate current management strategies, researchers conducted the UC Narrative global survey in 2020.[2] One strength of this study is its relatively large sample size, with investigators compiling and analyzing insights from more than 2000 patients and more than 1200 physicians. Investigators reported discordance between patients' and physicians' ranking of priorities in disease management. For example, reducing the risk of cancer ranked

second among patients in importance, whereas avoiding colectomy ranked second among physicians.[2] Although physicians understand that UC significantly disrupts patients' lives, many appear to underestimate the extent of this burden. Physicians surveyed in another study estimated that 35% of patients with UC have difficulty living a normal life and experience an average of 3.4 flares a year.[5] In that same assessment, 55% of patient respondents reported difficulty with ordinary daily life and reported an average of 5.5 flares a year **(Figure 1)**.[5]

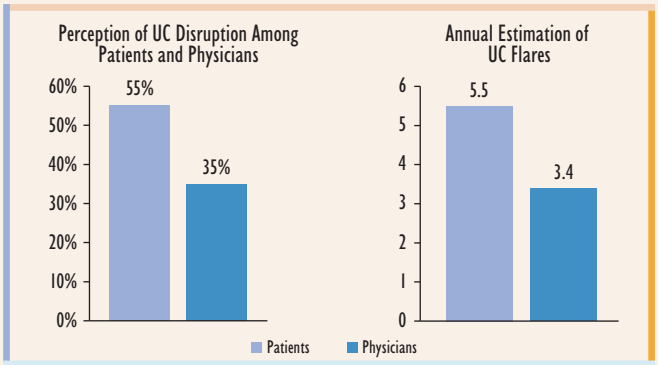

Figure 1. A substantial gap exists between patient and physician perception of disease burden in moderate to severe ulcerative colitis[5]

Abbreviation: UC, ulcerative colitis.

Additional findings from the 2020 UC Narrative global survey indicate that patients with UC achieve incomplete disease control with treatment.[2] These suboptimal outcomes with the current standard of care may possibly contribute to high rates of anxiety and depression among patients diagnosed with UC. Approximately two-thirds of patients (65%) interviewed believe that their condition controls their life, with a minority of respondents (37%) characterizing their overall health as "excellent" or "good". Furthermore, most physicians interviewed agreed with the notion that most patients in UC view pain and cramping as a part of living with their disease. Such low expectations for management mirror attitudes expressed in a previous investigation conducted in 2009.[6] In this study, 82% of 451 patient respondents stated that they had learned to cope with UC-associated disruptions and 88% believed that they would be dependent on medication for the remainder of their lives. Although no cure yet exists for UC, physicians have the ability to elevate patients' hopes for treatment and reduce their willingness to accept inferior outcomes. Without proper instruction, patients can mistake partial improvement on a prescribed therapy as the best possible outcome in UC.

Despite their prevalence, anxiety and depression do not always receive acknowledgement during routine clinical visits.[2] This issue originates to a degree from patient reluctance to initiate conversations on mental health matters. In one survey, approximately half (48%) of 2100 patients with UC felt uncomfortable discussing emotional concerns related to their condition.[3] Additionally, fewer than half (49%) of physicians participating in the UC Narrative global survey indicated that they discussed the emotional and mental dimensions of the disease with patients.[2] When engaging in conversations with patients, physicians may want to reorient their mindset away from objectives outlined in clinical guidelines (eg, mucosal healing, endoscopic improvement) and toward concerns relating to QOL. Furthermore, by probing these sensitive personal matters, physicians can possibly identify UC earlier in patients and minimize the length of diagnostic delays, which extend, on average, for 2 years. Prompt initiation of therapies is crucial because the risk of complications and UC-related intestinal surgery increases the later treatments are administered.

Tools to Improve Communication and Assess for Effects on Quality of Life

Several tools and strategies can improve the quality of communication between clinicians and patients diagnosed with UC. In addition to using disease activity indices, which gauge the degree to which clinical targets are being met, clinicians should consider incorporating patient-reported outcomes (PROs) into practice. In contrast with clinician-driven tools, PROs such as the 6-point Mayo score and PRO2 evaluate the patient's perspectives on disease activity and outcomes. Information collected from PROs can inform physicians' strategies to manage UC and identify the adverse effects detracting most from patient-related QOL. To glean even greater insights on patient status, clinicians should also consider adapting and customizing the questions within a given PRO. For example, when using the PRO2, clinicians do not need to necessarily limit their line of questioning to rectal bleeding and the number of stools. Probing for additional details, such as stool consistency and total attempts to defecate, can lead to more productive conversations and the discovery of other comorbid medical issues warranting further investigation.

Better use of patient advocacy organizations and digital tracking tools can also help close communication gaps between clinicians and patients with UC. In the UC Narrative global survey, 42% of all participants believed that an online tool or smartphone application tracking patient activities and symptoms would help improve interpersonal communication between physicians and patients.[2] The second most desired resource for improving interpersonal communication was advice on where to get reliable information that helps patients manage their disease. One viable option that can fulfill this need is a patient advocacy organization. Less than one-fourth of patients in the UC Narrative global survey stated that they had experience using a patient advocacy organization as an information source. Of those surveyed who had interacted with these organizations, most wished they had sought help from them earlier. Such entities can facilitate and structure patient education. Patient efforts to self-direct education regarding their condition, although laudable, are often challenged by the sheer amount of misinformation available online on UC. By connecting patients with reliable resources, clinicians can help ensure that patients cultivate a deeper understanding of their condition.

To optimize outcomes, gastroenterologists and supporting clinicians should work closely with patients to address factors detracting from their emotional well-being. Identifying the unmet individual needs of patients can inform clinician decisions on treatment and management.

TREATING MODERATE TO SEVERE ULCERATIVE COLITIS: REVIEW OF CURRENT GUIDELINES AND TREATMENT LIMITATIONS

David T. Rubin, MD

Just as the treatment landscape in moderate to severe UC has evolved, so too have the goals for patient management. According to the 2019 American College of Gastroenterology (ACG) guidelines, the diagnosis of UC should include extent of disease, histologic confirmation of chronicity, and some element of

prognosis.[7] Within UC, clinicians are also increasingly separating activity—a patient's present degree of sickness—from severity, which captures elements of a patient's prognosis. The emergence of new treatment options in UC has triggered a shift away from symptomatic disease control toward more ambitious objectives, such as endoscopic improvement and mucosal healing.[8] Concurrent with this change is an improved view on the role of maintenance therapy, which strives to prevent recurrence instead of treatment of active disease on a chronic basis. Although UC is formally a disease of the digestive tract, ACG guidelines are also placing a stronger emphasis on screening for mental health conditions, which manifest at a higher rate in patients with UC than in the general population. If executed properly, these goals should lead to lower costs of care, driven largely by reductions in the rates of hospitalization, infections, neoplasia, and drug-related problems.

Assessment of disease risk and activity has also transformed recently with the advent of the ACG UC Activity Index. Standard assessments of UC activity—using distinctions such as mild, moderate, and severe—are insufficient to guide selection of therapy.[9] A superior, more informative strategy is that of stratifying patients with UC into low- and high-risk categories for colectomy. Certain attributes, such as high C-reactive protein (CRP) level, low albumin level, infection with *Clostridioides difficile*, cytomegalovirus infection, and a history of hospitalization, all constitute actionable insights that can inform selection of a more aggressive treatment regimen.[7] The ACG UC Activity Index helps guide decision making. Unlike the Truelove and Witts severity index, this system gauges a patient's current status. This difference results in the addition of novel components, namely factors that define remission and the consideration of urgency across various severities of UC **(Table 1)**.[7] In addition to urgency, which is gaining rapid adoption, the ACG UC Activity Index incorporates 2 different endoscopic subscores and inflammatory biomarkers: CRP and fecal calprotectin (FCAL). Although no therapeutic biomarkers yet exist in UC, FCAL can serve as a surrogate for endoscopy when the procedure is not feasible to assess mucosal healing and disease activity.[7,10]

Table 1. American College of Gastroenterology Ulcerative Colitis Activity Index[7]

	Remission	Mild	Moderate to Severe	Fulminant
Number of stools per day	Formed stools	< 4	> 6	> 10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	< 75% of normal	Transfusion required
ESR	< 30	< 30	> 30	> 30
CRP, mg/L	Normal	Elevated	Elevated	Elevated
Fecal calprotectin, µg/g	< 150-200	> 150-200	> 150-200	> 150-200
Endoscopy (Mayo subscore)	0-1	1	2-3	3
UCEIS	0-1	2-4	5-8	7-8

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

Because there are no validated therapeutic biomarkers in UC, clinicians should adopt a treat-to-target strategy.[11] In this approach, clinicians first establish a baseline assessment of disease activity in patients and acquire a basic understanding of prognosis. From here, care providers form a benchmark of targets that correlate with endoscopy and explain the goals of therapy to the patient. When possible, there should be shared decision making in the initial selection of therapy, after which care providers can adjust therapy toward the target over time.[11,12] This process continues generally until the physician feels uncomfortable advancing therapy, if all options are depleted, or if the patient has no desire to receive further treatment. To guide the implementation of this approach, physicians can refer to the STRIDE-II consensus statement constructed by the International Organization for the Study of Inflammatory Bowel Diseases.[12] This statement outlines proposed targets for UC and divides them into short-term, intermediate, and long-term targets. Along with endoscopic healing, normalized QOL, and minimal disability, clinicians may want to consider histologic healing in UC as a long-term target. That said, debate continues regarding the feasibility of achieving this goal with patients.

Treatment Recommendations in the American College of Gastroenterology and American Gastroenterological Association Guidelines

Induction of remission is the immediate priority of treatment of moderate to severe UC. To this end, ACG guidelines recommend aminosalicylate (5-ASA) formulations as monotherapy or multimatrix system (MMX) budesonide for those patients with more moderate disease.[7,13] For UC that is refractory to these options or for patients whose disease is more advanced when treatment is initiated, evidence supports treatment selection among several drug classes, including systemic corticosteroids and several classes of biologics to induce remission.[7,13] Evidence supporting the use of anti–tumor necrosis factor (TNF) biologics—adalimumab, golimumab, and infliximab—stem mostly from the results of UC SUCCESS, a comparative effectiveness study, which revealed that the combination of infliximab and azathioprine is superior to either agent used in isolation when measuring steroid-free remission.[14] In the event of anti-TNF therapy failure, other biologics, such as vedolizumab or ustekinumab, and the nonselective Janus kinase (JAK) inhibitor tofacitinib are viable treatment choices.[7,13] According to the guidelines, vedolizumab and ustekinumab can also be used to induce remission in patients with moderate to severe UC. Methotrexate monotherapy, in contrast, has little evidence supporting its use in the induction setting and should be avoided.

In the maintenance setting, previous agents selected for induction should guide the use of subsequent therapy.[7,13] If corticosteroid formulations resulted in remission, ACG guidelines recommend thiopurines as a treatment option, although this class of medication has seen less use in recent years because of safety signals indicating a risk of lymphoma.[7] Alternatively, when anti-TNF therapies or other biologics succeed in the induction phase, physicians can continue use of the agent to maintain remission.[7,13] Tofacitinib, in particular, carries a label that permits either 5- or 10-mg twice-daily use during maintenance, with US Food and Drug Administration guidance encouraging dose reduction whenever feasible. Although useful in efforts to achieve initial disease control, corticosteroids can result in the development of serious, irreversible adverse events that should preclude their sustained use. Results from a prospective randomized trial also suggest against the use of methotrexate monotherapy for patients with UC who have achieved remission.[15]

Data gauging the comparative efficacy of biologics in UC remain limited, although some findings from the VARSITY trial can now inform therapeutic selection.[13,16] In this study, investigators assessed the clinical use of vedolizumab with that of adalimumab in patients with moderate to severe UC. After 52 weeks, 31.3% of 383 patients treated with vedolizumab achieved the trial's primary end point of clinical remission compared with 22.5% of 386 patients treated with adalimumab ($P = .006$). Notably, this significant trend stays intact even when stratifying patients into

anti–TNF treatment-naïve and treatment-exposed subgroups.[16] For patients escalated to anti-TNF biologics, evidence from observational studies indicate that concomitant 5-ASA does not modify outcomes in patients receiving advanced therapies, namely anti-TNF biologics or tofacitinib.[17] Continuation of therapy most likely adds to the cost and complexity of care while possibly raising the probability of treatment nonadherence. As such, physicians may want to streamline care by withdrawing 5-ASA therapy to simplify regimens for patients.

Differences Between American College of Gastroenterology and American Gastroenterological Association Clinical Guidelines

Clinical practice guidelines published by the ACG in 2019 and the American Gastroenterological Association (AGA) in 2020 are largely concordant, but differ on several matters.[7,13] In particular, ACG guidelines do not stratify treatment options for biologic-naïve patients, whereas AGA guidelines establish a hierarchy. ACG guidelines also predate the publishing of the VARSITY trial results, which justify the use of infliximab or vedolizumab over adalimumab in biologic treatment–naïve patients with moderate to severe UC.[16] Similarly, because ustekinumab had not yet gained approval at the time of its publication, the 2019 ACG guidelines did not list the agent as an option in the event of treatment failure on anti-TNF therapy.[7] The 2020 AGA guidelines, in contrast, recommend ustekinumab or tofacitinib rather than vedolizumab or adalimumab for the induction of remission in patients with primary nonresponse to infliximab.[13] **Table 2** summarizes these key differences, along with others relating to tofacitinib and methylprednisolone dosing.[7,13] As is often the case once guidelines are released, recommendations on the use of newly approved agents are not addressed and await inclusion in the next set of guidelines. This is evident in the lack of guidance in both the ACG and AGA guidelines on the use of ozanimod to treat patients with UC.

Table 2. Key Differences Between the 2019 American College of Gastroenterology and the 2020 American Gastroenterological Association Guidelines

Setting	2019 ACG Guidelines[7]	2020 AGA Guidelines[13]
Tofacitinib	Label change for safety had not yet occurred	Biologic-naïve patients should only be treated in research
First-line therapy in biologic-naïve patients	Infliximab, adalimumab, golimumab, or vedolizumab	Infliximab or vedolizumab, rather than adalimumab
Infliximab-exposed patients	Vedolizumab or tofacitinib; guideline written before approval of ustekinumab	Ustekinumab or tofacitinib, rather than vedolizumab or adalimumab
Hospitalized ulcerative colitis	60 mg/d of intravenous methylprednisolone	40-60 mg/d of intravenous methylprednisolone

Abbreviations: ACG, American College of Gastroenterology; AGA, American Gastroenterological Association.

Limitations of Biologic Therapies in Ulcerative Colitis

Although anti-TNF therapies can help patients achieve and maintain remission in UC, biologic therapies possess several notable limitations. In clinical trials, between 19% and 58% of patients experience primary failure on anti-TNF induction therapy.[1] Among patients responsive to anti-TNF therapies, discontinuation due to secondary loss of response occurs in 17% to 22% of patients, and approximately 40% require dose escalation to maintain treatment efficacy.[1] Diminishing efficacy stems, in part, from immunogenicity and the formation of antibodies against biologics. Chronic use of anti-TNF therapies may induce a panoply of treatment-emergent adverse effects (TEAEs), most notably lymphoma.[18] Because anti-TNF therapies are immunosuppressive, the likelihood of opportunistic bacterial and fungal infections rises. Clinicians have previously observed paradoxic immune reactions, lupoid-type reaction, and pustular psoriasis in patients on long-term anti-TNF agents. Reactivation of latent tuberculosis can additionally prove particularly problematic in patients residing in developing countries with more limited medical infrastructure.

Alternative monoclonal antibodies, namely vedolizumab and ustekinumab, and the pan-JAK inhibitor tofacitinib possess their own set of drawbacks. Vedolizumab, as an α4β7 integrin antagonist, has little to no effect outside the digestive tract and cannot prevent extraintestinal manifestations of disease.[19] In contrast, ustekinumab use may result in joint pain and injection-related reactions.[20] As a pan-JAK inhibitor, tofacitinib acts against all 4 JAK isoforms that participate in the immune response against certain viruses. Consequently, investigators have noted in clinical trials that tofacitinib use raises the risk of herpes zoster infection, along with the likelihood of other serious opportunistic infections.[21] More recent safety data from a phase 4 trial of tofacitinib in patients with rheumatoid arthritis have also raised serious safety concerns.[22] In particular, the findings indicate that tofacitinib use raises the probability of developing serious cardiovascular-related complications, such as venous thromboembolism, and malignancy. Although these results cannot yet be extrapolated to patients with UC or other autoimmune disorders, additional safety data are currently pending on other potential complications, such as blood clots in the lungs and even death.[23] Taken together, these limitations necessitate the integration of newer-generation therapies for patients with UC that are safe, effective, tolerable, and easily administered.

SPHINGOSINE-1-PHOSPHATE MODULATORS IN ULCERATIVE COLITIS

William J. Sandborn, MD

High rates of nonresponse to existing therapies necessitate the development of new options that can improve disease control in moderate to severe UC. According to 1 survey, approximately half of patients (48%) feel dissatisfied with their current treatment regimen.[24] In this study cohort, participants identified onset of action, efficacy, and tolerability as the most valuable attributes of medication for UC. Beyond these factors, patients also tend to prefer orally administered therapies because of their ease of use[25]; intravenously delivered medications can inconvenience patients, who must travel periodically to infusion centers to receive treatment. This key advantage, in part, contributes to growing interest in oral small molecule drugs for UC among clinicians and researchers. Several classes of drugs acting against JAK, phosphodiesterase-4, and the sphingosine-1-phosphate (S1P) receptors exist within this growing family of medications.[26] Compared with biologics, these agents have a lower cost associated with their production, transportation, and storage, along with reduced immunogenicity.[27] Additionally, oral small molecules have shorter half-lives than do intravenously administered biologics. Consequently, these medications can be used in start-stop dosing strategies to control flares in UC and may have fewer adverse effects upon discontinuation.[28] The most notable disadvantages are polypharmacy and frequent dosing; physicians must rely on patients to take prescribed oral medication at recommended intervals.[29]

Among the most transformative agents in development for the treatment of UC are S1P modulators. Functionally, S1P is a signaling phospholipid secreted by erythrocytes, endothelial cells, and platelets into the extracellular environment. Transported by apolipoprotein M and albumin, S1P can bind 5 G-coupled protein receptor isoforms (S1PR1-S1PR5) and mediates a diverse number of biologic processes **(Table 3)**.[30] S1P modulators exert immunomodulatory effects by binding different classes of S1PRs and promoting their internalization. By downregulating S1PR expression, these agents effectively trap activated lymphocytes in secondary lymphoid organs, such as lymph nodes. Ordinarily, S1P-mediated signaling promotes lymphocytic egress and pathologic immune cell migration to peripheral tissues, including those of the intestine.[31] Members of this treatment family, such as fingolimod, ozanimod, siponimod, and ponesimod, have been investigated and approved within the last decade in the context of multiple sclerosis **(Table 4)**.[30,32–34]

Table 3. Sphingosine-1-Phosphate Receptor Sites of Expression, Function, and Clinical Relevance[30]

	Expression	Biological Outcomes	Clinical Relevance
S1PR1	Broad, including B, T, and dendritic cells, endothelium, cardiac tissue, and neurons	Lymphocyte migration, dendritic cell migration, vascular barrier function, bradycardia, nociception, proliferation	Autoimmune modulation, bradycardia, tumor maintenance
S1PR2	Broad, including vascular smooth muscle, endothelium, cardiac tissue, lung fibroblasts, and tumor cells	Vasoconstriction, inflammation, fibrosis, inhibition of B cell survival, proliferation	Renal injury, fibroblast contraction, tumor maintenance
S1PR3	Broad, including vascular smooth muscle, endothelium, cardiac tissue, and lung fibroblasts	Vasoconstriction, fibrosis, proliferation	Hypertension, tumor maintenance
S1PR4	Restricted; T cells, dendritic cells, breast cancer cells	Inhibition of effector cytokines, secretion of interleukin-10	Autoimmune modulation
S1PR5	Restricted; natural killer cells, endothelial cells, oligodendrocytes	Natural killer cell migration, blood-brain barrier integrity, oligodendrocyte function	Autoimmune modulation, myelination

Abbreviation: S1PR, sphingosine-1-phosphate receptor.

Note: S1PR1, S1PR4, and S1PR5 are implicated in autoimmune modulation and represent therapeutic targets in conditions such as ulcerative colitis.

Table 4. Indication, Receptor Selectivity, and Approval Status of Sphingosine-1-Phosphate Receptor Modulator Drugs

Drug	Indication	Receptor Selectivity	Status
Fingolimod[30]	MS	S1PR1, S1PR3, S1PR4, S1PR5	FDA approved 2010
Siponimod[30]	MS	S1PR1, S1PR5	FDA approved 2019
Ozanimod[32,33]	MS, UC	S1PR1, S1PR5	FDA approved 2020 (MS), FDA approved 2021 (UC)
Ponesimod[34]	MS	S1PR1	FDA approved 2021

Abbreviations: FDA, US Food and Drug Administration; MS, multiple sclerosis; S1PR, sphigosine-1-phosphate receptor; UC, ulcerative colitis.

Just as the S1PRs differ in their distribution and function, so too do the S1P modulators vary in their selectivity. Fingolimod, the first approved S1P modulator, targets all S1PRs except S1PR2.[27] This broader mechanism of action limits the drug's use because it leads to substantial adverse events such as macular edema, bradycardia, atrioventricular blocks, high blood pressure, liver injury, and even basal cell carcinoma.[35] These highly undesirable effects stem from fingolimod acting on S1PRs expressed by the heart and vasculature.[27] Newer agents, such as ozanimod and etrasimod, do not activate S1PR2 and S1PR3 and are therefore associated with less severe treatment-related cardiovascular complications. Ozanimod selectively targets S1PR1 and S1PR5, whereas etrasimod exhibits selectivity for S1PR1, S1PR4, and S1PR5.[24] Both agents have undergone extensive investigation through phase 2 and 3 trials in patients with moderate to severe UC. Results from these studies have helped clarify the distinguishing attributes between ozanimod and etrasimod in patients with moderate to severe UC.

Degrees of lymphocytic suppression, half-life, and dosing all differ between ozanimod and etrasimod. In healthy volunteers, ozanimod resulted in an approximate 65% reduction of lymphocytes at a dose of 1 mg, whereas etrasimod led to a 67% median reduction in lymphocyte counts at a dose of 2 mg.[36,37] When assessing its effects in populations with inflammatory bowel disease, investigators observed that 1 mg of ozanimod led to a 50% suppression of lymphocytes after 8 weeks of therapy.[38] By direct comparison, 2 mg of etrasimod led to 40% suppression.[39] The half-life of ozanimod's phosphorylated metabolite is 11 days and takes some time to accumulate before pharmacodynamic effects manifest. Etrasimod, in contrast, has a shorter half-life of 33 hours and lacks a long-acting metabolite. Consequently, lymphocyte levels normalize relatively quickly—approximately 7 days within treatment cessation.[37] Finally, heart rate reductions are more pronounced with ozanimod than with etrasimod; patients receiving ozanimod require dose titration, whereas those receiving etrasimod can move straight to the target dose of 1 or 2 mg without titration.

In the phase 2 TOUCHSTONE trial, investigators evaluated the safety and efficacy of ozanimod 0.5 and 1 mg once daily against placebo in patients with moderate to severe UC.[38] At 8 weeks, 16% of patients (11/67) receiving 1 mg of ozanimod reached clinical remission vs 6% of those receiving placebo ($P = .048$). Researchers observed further significant differences in favor of ozanimod, especially at the 1-mg dose, for clinical response and histologic remission at week 32. A significant proportion of patients partaking in the open-label extension of the phase 2 TOUCHSTONE study also derived continued benefit from ozanimod.[40] When using nonresponder imputation, 41.2% of 170 patients had a clinical response and 36.5% of 170 patients were still in clinical remission. A single patient in the ozanimod 0.5-mg group with evidence of preexisting bradycardia discontinued treatment after experiencing a first-degree atrioventricular block at day 8. Another 4 patients had liver enzyme levels 3 times the upper limit of normal. Beyond these events, most treatment-related adverse events with ozanimod were relatively mild, typically consisting of anemia and headache.

For the phase 3 True North study, investigators randomly assigned adults with moderate to severe UC to receive oral ozanimod 1 mg once daily (n = 429) after a 1-week dose escalation period or placebo (n = 216) for a 10-week induction period **(see page 9 – Ozanimod and Etrasimod Phase 3 Study Designs: Key Points)**.[41] At week 10, 18.4% of patients receiving ozanimod experienced clinical remission vs 6% of patients receiving placebo **(Figure 2)**.[41] Beyond being 3 times as effective in inducing remission, ozanimod also led to statistically significant improvement in all secondary end points measured. Patients receiving ozanimod maintained these gains and had a higher likelihood of being in clinical remission and exhibiting endoscopic improvement at week 52 than those receiving placebo. During the trial, investigators did not detect any new safety signals and found the treatment to be generally well tolerated. Rates of TEAEs

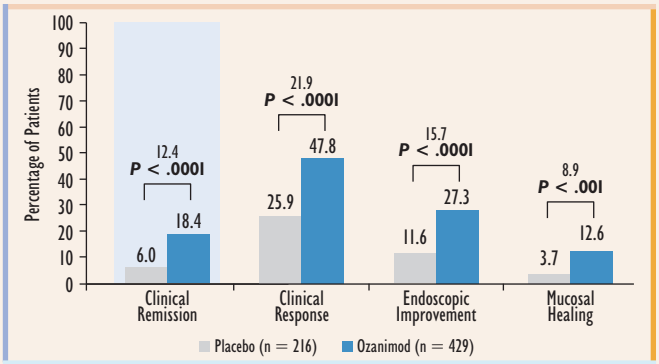

Figure 2. In the phase 3 True North study, a greater proportion of patients receiving ozanimod 1 mg experienced clinical remission at the end of the 10-week induction period than those receiving placebo[41]

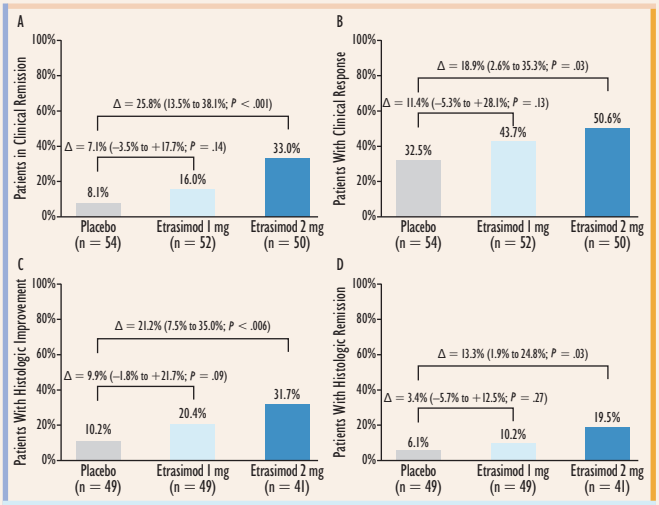

Figure 3. In the phase 2 OASIS trial, 33% of patients receiving etrasimod 2 mg experienced clinical remission vs 8.1% patients receiving placebo (A).[39] Significant differences between the etrasimod 2-mg and placebo groups were also noted for clinical response (B), histologic improvement (C), and histologic remission (D).

were higher with ozanimod (49.1%) than with placebo (38.6%), with anemia, nasopharyngitis, and headache being the most common issues.[41,42] On the basis of these results, ozanimod received US Food and Drug Administration approval in May 2021 and represents the first S1P modulator approved for patients with moderately to severely active UC.[33]

Similar to ozanimod, etrasimod has demonstrated considerable therapeutic activity in multiple studies.[39,43] In the phase 2 OASIS trial, investigators assessed the clinical use of etrasimod 1 mg (n = 52) and 2 mg (n = 50) once daily vs placebo (n = 54) in patients with moderate to severe UC.[39] The primary end point was an increase in the mean improvement of modified Mayo scores from baseline to week 12. At week 12, 33% of patients receiving etrasimod 2 mg achieved clinical remission compared with 8.1% of patients receiving placebo ($P < .01$) **(Figure 3)**.[39] In addition, the modified Mayo score significantly improved at week 12 with etrasimod 2 mg compared with placebo ($\Delta = 0.99$; $P = .009$). Endoscopic improvement, a secondary end point of the trial, also manifested in a greater proportion of patients receiving etrasimod 2 mg than in those receiving placebo. Most patients (75%) treated with etrasimod 1 or 2 mg once daily experienced mild and moderate TEAEs, such as upper respiratory tract infections, nasopharyngitis, and anemia.

Encouraging findings from the OASIS trial prompted an open-label extension of the study that assessed the durability of patient responses on etrasimod.[43] For an additional 34 to 40 weeks, 112 patients previously enrolled in OASIS continued to receive etrasimod 2 mg once daily and were observed by investigators for safety and efficacy. At the end of treatment, 64% of patients fulfilled the criteria for clinical response, 43% experienced endoscopic improvement, and 33% reached clinical remission. Furthermore, among patients with a clinical response, clinical remission, or endoscopic improvement at week 12 in OASIS, most maintained their status. Steroid-free clinical remission, a goal of treatment guidelines, occurred in 22% of patients overall. Although 60% of patients receiving etrasimod 2 mg experienced TEAEs, 94% of 252 adverse events were mild or moderate in nature. During the open-label extension, researchers observed no new safety signals or serious infections linked to treatment.[43] A randomized, double-blind phase 3 trial, ELEVATE UC 52 **(see page 9 – Ozanimod and Etrasimod Phase 3 Study Designs: Key Points)**, is under way to evaluate the safety and efficacy of etrasimod 2 mg in patients with moderate to severe UC.[44]

CASE 1: BIOLOGIC-NAÏVE PATIENT WITH ULCERATIVE COLITIS

From the Files of Marla C. Dubinsky, MD

A 23-year-old male was diagnosed with left-sided UC 18 months ago and was treated with 4.8 g of mesalamine. He presented with moderate cramping and occasional urgency, along with 5 to 6 loose bowel movements. Blood was present in approximately 50% of the stools. Normal CRP level is noted, as well as slightly low hemoglobin level (11.8 g/dL) and elevated FCAL level (980 µg/g). Albumin level was within its expected range (3.7 g/dL). Results from a full stool workup were normal. He also had a colonoscopy, which showed continuous Mayo score of 2 from rectum to splenic flexure and consistent pathology to match the macroscopic appearance. At follow-up, he is seeking advice from physicians on what additional therapeutic options are available.

Discussion

Dr Dubinsky: With the therapies that we have, how would you manage this patient?

Dr Rubin: Given his endoscopic appearance and anemia, I am less enthusiastic about the prospect of adding a rectal mesalamine to get him over the hump. I would be moving toward a steroid approach at this point. The guidelines would suggest budesonide MMX as the oral formulation here. I do not think we would be able to back down to 5-ASA and maintenance therapy.

Dr Dubinsky: Let us assume for the sake of discussion that the oral topical approach was not working. Out of all of the therapies we have right now, what would drive you to choose one therapy over another? We have a biologic and a small molecule available. How would you interpret the data, and decide?

Dr Rubin: For patients needing steroids, guidelines recommend the use of a steroid-sparing therapy. Specifically, the suggestion is to use duct-selective therapy if there are no other contraindications to it. Right now, vedolizumab would fulfill that requirement, and it has been adopted in both our practice and in other places around the world.

Dr Dubinsky: Dr Sandborn, how would you position S1P modulators in light of Dr Rubin's answer? Do you have any additional thoughts on what therapies may be appropriate for this patient?

OZANIMOD AND ETRASIMOD PHASE 3 STUDY DESIGNS: KEY POINTS

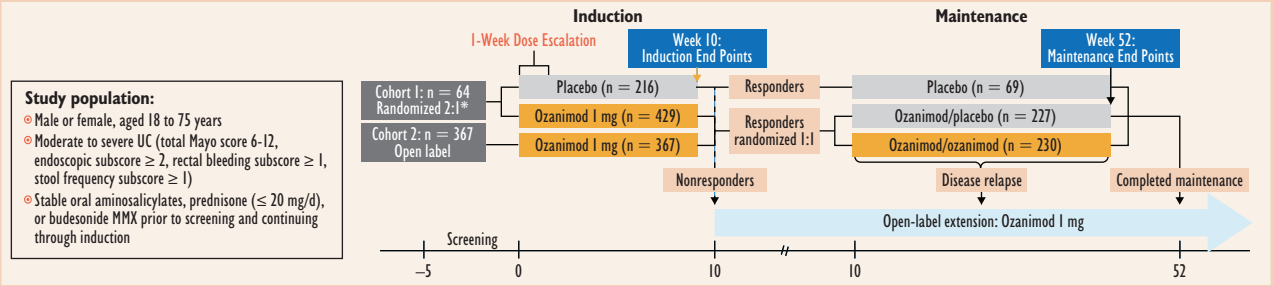

Figure 1. Ozanimod phase 3 study design[1]

Abbreviations: MMX, multimatrix system; UC, ulcerative colitis.
* Patients in cohort 1 were stratified by prior anti-TNF use and corticosteroid use prior to randomization

- The True North study was a phase 3, double-blind, randomized trial consisting of a 10-week induction period followed by a maintenance period lasting until week 52.[1] The trial assessed the clinical efficacy of ozanimod 1 mg once daily vs placebo in patients with moderately to severely active ulcerative colitis (UC).
- Adult patients aged between 18 and 75 years in the True North study were enrolled into cohort 1 or cohort 2. Adolescent patients aged < 18 years were placed in cohort 3.
- The inclusion criteria for the True North study include UC confirmed on endoscopy, moderately to severely active UC (Mayo score of 6-12), and current treatment with aminosalicylate, prednisone, or budesonide
- For the induction period, patients in cohort 1 were randomly assigned 2:1 to receive ozanimod 1 mg or placebo, with randomization being stratified by prior tumor necrosis factor inhibitor use and corticosteroid use at screening
- Patients who exhibited a clinical response at the end of the induction period proceeded to the maintenance phase and were randomly assigned 1:1 to receive ozanimod 1 mg or placebo
- The primary end points of the True North study were the proportions of patients in clinical remission at the end of the induction period (week 10) and maintenance period (52 weeks). Clinical remission was defined as rectal bleeding subscore of 0, stool frequency subscore ≤ 1, decrease of ≥ 1 point from baseline stool frequency subscore, and endoscopy score ≤ 1.
- Patients from cohorts 1 to 3 who participated in the True North study were eligible to participate in an optional open-label extension trial

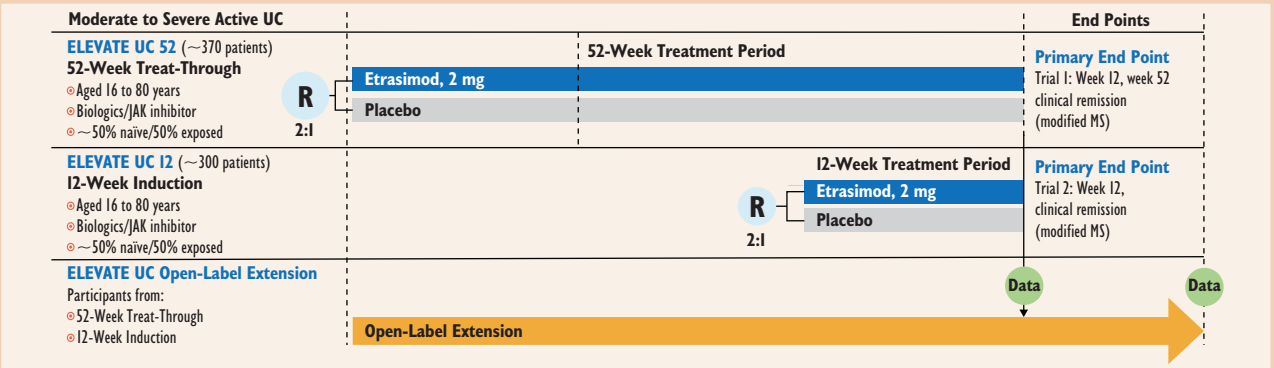

Figure 2. Etrasimod phase 3 study design[2-4]

Abbreviations: JAK, Janus kinase; MS, Mayo score; R, randomization; UC, ulcerative colitis.

- ELEVATE UC 52 was a phase 3, randomized, double-blind, 52-week treat-through clinical trial gauging the safety and efficacy of oral etrasimod 2 mg once daily in patients with moderately to severely active UC[2]
- The primary end points of the ELEVATE UC 52 trial were the proportions of participants achieving clinical remission as assessed by Mayo scores at weeks 12 and 52
- The inclusion criteria for ELEVATE UC 52 included a diagnosis of UC 3 months prior to screening and active UC confirmed by endoscopy. Patients eligible for treatment were aged between 16 and 80 years.
- ELEVATE UC 12 was an induction trial whose design resembled that of ELEVATE UC 52 but lasted only 12 weeks[3]
- The ELEVATE UC OLE trial will enroll participants from the ELEVATE UC 52 and ELEVATE UC 12 trials.[4] Findings from this study will provide greater clarity on the long-term safety and efficacy of etrasimod.

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Dr Sandborn: If the patient is willing to take parenteral therapy, then I think that Dr Rubin's selection of vedolizumab is an excellent choice. I also think that ustekinumab is quite safe and would work in this context. For patients who desire oral therapy, the S1P modulators, such as ozanimod, are going to be good choices here. To date, there is not a signal for malignancy, and the S1P modulator class of treatments has been well tolerated in patients with conditions other than inflammatory bowel disease. Regarding alternatives, oral therapy with tofacitinib is not permitted in this setting because of its safety profile. JAK1 selective therapy could fit here as well, but it is a class of drugs for which we are still awaiting safety data at higher doses.

Take-Home Points

- Route of administration can influence treatment selection in instances in which multiple treatment options are feasible
- Orally administered S1P modulators are generally well tolerated in patients and do not carry a risk of malignancy, which is a concern among patients with moderate to severe ulcerative colitis

CASE 2: ANTI–TUMOR NECROSIS FACTOR-REFRACTORY PATIENT WITH ULCERATIVE COLITIS

From the Files of Marla C. Dubinsky, MD

A 29-year-old female was diagnosed with pancolitis 7 months ago and was treated with 40 mg of weekly adalimumab. Despite treatment, the patient reported 7 to 8 bowel movements daily, along with moderate cramping, tenesmus, urgency, and blood in most stools. Laboratory test results reveal low hemoglobin (10.4 g/dL), low albumin (3.3 g/dL), and abnormally elevated CRP (10.2 mg/L) and FCAL levels (1500 µg/g). Results from infection stool studies were normal. A colonoscopy revealed Mayo score of 3 for the first 25 cm, then Mayo score of 2 until the cecum. Histopathology confirms pancolitis with normal terminal ileum biopsies. During another evaluation, the patient reported a scaly rash on her scalp and palms and a desire to become pregnant in the next 12 months.

Discussion

Dr Dubinsky: What are your thoughts on how to sequence treatments for this patient?

Dr Rubin: The details of the case suggest that the patient has developed a palmar-plantar pustulosis, perhaps as a consequence of her previous therapy with an anti-TNF agent. My focus would be to get her into deep remission immediately, then consider a transition to an alternative therapy in maintenance. At that point, the idea of a pregnancy can be revisited. I am primarily worried about dragging her along with severe colitis on another monoclonal antibody and not necessarily getting to where we need her to go. As a result, I would consider and propose tofacitinib in this scenario because we can tell within a couple of weeks if it is working. In the maintenance setting, I think transitioning to ustekinumab or even vedolizumab would be appropriate.

Dr Dubinsky: If this patient was on weekly adalimumab, would you switch to an alternative anti-TNF therapy such as infliximab? Is it an option to not give up on the anti-TNF treatment class? Could you provide some additional guidance on how to possibly incorporate S1P modulators?

Dr Sandborn: Intensive intravenous dosing with infliximab can sometimes work when adalimumab has not worked, so in this instance, another anti-TNF therapy could be appropriate. Potential teratogenicity issues preclude the use of JAK inhibitors in patients desiring to become pregnant, and these concerns extend to S1P modulators. It is not a class of drugs you want to prescribe to a female desiring conception. In the absence of pregnancy, ozanimod could work here; that said, results from clinical trials indicate that it is a little bit slower to act, particularly in patients who experienced failure on anti-TNF therapies. As a result, you may need a bridging induction strategy if you want to make an S1P modulator work with this patient and in patients in whom anti-TNF therapies have failed.

Take-Home Points

- Ulcerative colitis is a younger-onset disease in which proper sequencing of treatments is essential, particularly in patients planning a pregnancy
- S1P modulators are slower to act in patients in whom anti-TNF therapy previously failed than in those who are treatment naïve

KEY TAKEAWAYS AND CONCLUSIONS

- Gastroenterologists and supporting clinicians caring for patients with UC should ensure that expectations for treatment are aligned. Effective use of digital smartphone-based applications and other innovative tools can facilitate communication between parties and can minimize the risk of patients tolerating suboptimal outcomes from treatment.
- Lines of inquiry from the PRO2 questionnaire and other assessment tools can be expanded upon by clinicians to gain insight into symptoms that detract most from patient-related QOL. Adequately addressing the emotional dimension of UC is an important part of the comprehensive care strategy for UC.
- Biologic therapies for UC have several limitations, namely immunogenicity, adverse effects, and a relatively inconvenient form of administration. Thiopurines, an older treatment option, are being replaced in UC because their use is associated with the risk of developing lymphoma.
- Guidelines published by the ACG and the AGA are largely aligned, but differ in their treatment of tofacitinib, treatment sequencing in infliximab-exposed patients, and treatment selection in biologic-naïve patients
- Ozanimod and etrasimod are S1PR modulators that can effectively treat patients with moderate to severe UC. The recent approval of ozanimod and the possible approval of additional orally administered agents in this class are poised to transform treatment paradigms in moderate to severe UC.

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1. Which of the following is NOT included in the traditional Mayo score for clinical trials of UC?
   a. Rectal bleeding
   b. Endoscopy findings
   c. Rectal urgency

2. Which treatment class should be avoided for maintenance in patients with moderate to severe UC?
   a. Systemic corticosteroids
   b. Thiopurines
   c. Anti-TNFs

3. What percentage of patients achieved clinical remission during the induction period of the phase 3 True North study of ozanimod?
   a. 6.0%
   b. 18.4%
   c. 56.0%

4. What percentage of patients achieved clinical remission during the induction period with etrasimod 2 mg in the phase 2 OASIS study?
   a. 12.2%
   b. 33.0%
   c. 58.4%

5. A 33-year-old male was diagnosed with severe pancolitis 16 months prior. He was treated with 9 mg of oral budesonide MMX at the time of diagnosis and, after 16 weeks, was switched to 40 mg of adalimumab. After having a good clinical response and normalization of stools for approximately 1 year, he currently reports having up to 6 bloody stools per day, an elevated CRP level, FCAL of 375 mg/g, and an endoscopic Mayo score of 3. Adalimumab serum level is 20 µg/mL without the presence of antibodies. He is negative for enteric infections and has expressed a desire to no longer self-inject medications or receive infusion therapy. Which of the following available treatments for UC would best align with this patient's goals of care?
   a. Infliximab
   b. Ustekinumab
   c. Tofacitinib

6. In the phase 3 True North study, which 3 TEAEs were the most common in patients receiving ozanimod compared with those receiving placebo?
   a. Headache, nausea, anemia
   b. Anemia, nasopharyngitis, headache
   c. Nausea, vomiting, diarrhea

7. In the open-label extension of the OASIS trial, what proportion of patients receiving etrasimod 2 mg experienced TEAEs?
   a. 60%
   b. 70%
   c. 80%

8. Lymphoma is a long-term TEAE associated with _____ treatment in UC.
   a. Budesonide
   b. Methotrexate
   c. Thiopurine

9. Ozanimod and etrasimod are S1P modulators not associated with serious treatment-related cardiovascular issues because they exclude the targeting of:
   a. S1PR2, S1PR3
   b. S1PR3, S1PR4
   c. S1PR1, S1PR4

10. A patient experiences primary nonresponse to infliximab. According to the 2020 AGA guidelines, which of the following treatments is the most appropriate for the induction of remission for this patient?
    a. Adalimumab
    b. Ustekinumab
    c. Oral budesonide MMX