ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Management of Patients With Refractory Ulcerative Proctitis

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G&H What is the current understanding of the relationship between ulcerative proctitis and ulcerative colitis?

MC Ulcerative proctitis is part of the disease spectrum of ulcerative colitis. Ulcerative proctitis is ulcerative colitis (inflammation) limited to the rectum, whereas more extensive ulcerative colitis can encompass any extent of the colon above the rectum. There is fairly frequent misunderstanding about these nuances in the medical community, as some providers think that ulcerative proctitis and ulcerative colitis are different conditions. In reality, ulcerative proctitis is part of the disease spectrum of ulcerative colitis; they have the same pathogenetic mechanism and the same immunologic background. In some cases, ulcerative colitis is limited to the rectum and thus was called ulcerative proctitis. Except for the extent of inflammation, there are no other differences between ulcerative proctitis and more extensive colitis. Educating our colleagues and patients about what ulcerative colitis means is important, as is looking at the colon as a whole organ. There may be some physiologic differences between the rectum and the rest of the colon, but pathologically ulcerative colitis is one continuous process with different extents, which in medicine are referred to as phenotypes: proctitis, left-sided colitis, extensive colitis, and pancolitis. Furthermore, mechanistically the underlying process that leads to disease development is the same, an overactive immune response against something within the colon and likely a loss of tolerance toward bacteria living inside the colon. Why the disease process extends more or less in different people is still unknown.

G&H How is refractory ulcerative proctitis typically defined?

MC Conventionally, it was defined based on failure of topical therapy. For many decades before 2000, the mainstay of treatment for ulcerative proctitis was topical therapy, either mesalamine or corticosteroids. Even though ulcerative proctitis represents 20% of ulcerative colitis cases, it has been neglected or underrepresented in clinical trials because the vast majority of those involving oral or advanced therapies (biologics and small molecules) have excluded patients with ulcerative proctitis. The research community has had a very ambivalent attitude toward ulcerative proctitis. On the one hand, we were saying that ulcerative proctitis is part of the spectrum of ulcerative colitis, so separate trials were not needed. On the other hand, we excluded ulcerative proctitis patients from most clinical trials because of their limited disease. That led to the conceptual fallacy that limited disease means mild disease, which is not true. At Digestive Disease Week 2024, my colleagues and I presented research showing that approximately 10% to 20% of patients with ulcerative proctitis require an advanced therapy, which is not dissimilar to patients with more extensive ulcerative colitis.

G&H Could you expand on why there was a lack of high-quality clinical trials in patients with ulcerative proctitis?

MC This, in my opinion, was an interesting bias. In the late 1980s in the first trials with oral mesalamine, which was the first type of treatment for mild to moderate

ulcerative colitis, researchers noticed that oral mesalamine was not more effective than placebo for ulcerative colitis limited to the rectum. Patients with ulcerative proctitis were then excluded from those trials to make the efficacy data look better. This approach was followed for the next 30 years without considering that newer therapies, which are systemically effective, might be efficacious for all patients with ulcerative colitis regardless of disease extent. Because of this rubber-stamp phenomenon, essentially replicating study design from one trial to another, patients with ulcerative proctitis ended up being severely underrepresented or ignored in clinical trials owing to a prevailing and grossly unfounded severity or efficacy bias.

G&H Why might topical treatments be preferred over oral or parental treatments?

MC One reason is effectiveness. The local concentration achieved with topical therapy likely exceeds the concentration obtained with some of the common oral therapies, and that applies to any form of ulcerative colitis. Any treatment a patient takes by mouth, and that does not work systemically by absorption, has to travel 18 to 20 feet to reach the colon. In contrast, rectal topical therapies are essentially placed at the site of action. Topical therapies generally have been quite effective for mild to moderate ulcerative proctitis, but the same products in oral forms are not quite as effective for more extensive ulcerative colitis, especially at healing the colon. That ended up being a mixed blessing. On one hand, the good response to topical therapies obviated the need for superior treatments, but on the other hand, it left 10% to 20% of these patients with more severe disease without any treatment because of the lack of guidance from clinical studies.

G&H Which topical agents have been best studied in patients with refractory ulcerative proctitis?

MC In patients with ulcerative proctitis that does not respond to topical mesalamine or corticosteroids, 2 relatively small clinical trials with another topical therapy called tacrolimus offered a new option. However, this therapeutic approach is nonconventional because tacrolimus is not approved for this indication and therefore is considered off-label. In addition, the product, topical tacrolimus, has to be compounded by a pharmacy. This was essentially a case of evidence without eminence. Despite obvious advantages, such as lack of or limited systemic exposure, rectally administered tacrolimus has very modest absorption but high local activity and ended up being used mostly in specialized centers by select clinicians.

G&H Are there any recent data on the use of thiopurines in this patient population?

MC The data are not very recent, but there are some studies in the past 2 decades with disappointing results. The results were actually inferior to what we even see in patients with more extensive ulcerative colitis. I suspect this is because those patients probably had more severe disease. In a study from France, only 20% of patients experienced benefit after the first year. The trial was not placebo-controlled. That type of data was what made people abandon the idea of using thiopurines for ulcerative proctitis. However, what was interesting about this study was that 1 out of 10 patients in that cohort ended up undergoing a colectomy. This highlights the fact that ulcerative proctitis can be a very severe disease. These patients can have very complicated clinical courses, just like patients with more extensive disease. As clinicians, it is important not to trivialize ulcerative proctitis patients.

G&H Which advanced therapies have been studied for the treatment of ulcerative proctitis?

MC The only one that has been studied in a clinical trial thus far is the sphingosine-1 phosphate (S1P) receptor modulator etrasimod (Velsipity, Pfizer) in the ELEVATE trial. This class of drugs was approved in ulcerative colitis 3 years ago, but etrasimod was the first systemic advanced therapy in the past 3 decades to undergo a clinical trial that included patients with ulcerative proctitis. Even though the percentage of patients with ulcerative proctitis was relatively small, roughly 10% of the trial population, the results for etrasimod in the ulcerative proctitis group were at least as good as those for patients with more extensive ulcerative colitis. Including patients with ulcerative proctitis may have looked risky at that time for many investigators, but the results were highly rewarding.

G&H Is there a role for appendectomy in the management of refractory ulcerative proctitis?

MC That idea comes from a small trial from Australia of patients who had relatively refractory ulcerative proctitis, with 10% not responding to or having inadequate response to biologics. After undergoing an appendectomy, 40% of patients entered remission. However, that trial was not replicated and is not part of mainstream algorithms. In general, practitioners are reluctant to send a patient for appendectomy for a perfectly normal appendix, especially since surgeons are frequently not familiar with this literature. This treatment approach was not embraced by the global community. I believe it is still in practice in

Australia, where the trial originated, as well as in some parts of Asia. It is not common or part of any standard in the United States or Western Europe.

G&H What other studies should be noted involving the management of refractory ulcerative proctitis patients?

MC Most of the evidence on the benefit of newer therapeutics in ulcerative proctitis comes from small-scale retrospective studies with therapies that include biologics. There are data on anti–tumor necrosis factor agents that show effectiveness in refractory ulcerative proctitis patients similar to that in patients with more extensive ulcerative colitis, but that research involved noncontrolled trials. That is why the ELEVATE trial was a significant breakthrough; it was a controlled, randomized clinical trial that included ulcerative proctitis patients. The evidence from retrospective analyses is weakened by biases and limitations, but it does suggest that biologics and other small molecules such as tofacitinib (Xeljanz, Pfizer) are also effective for ulcerative proctitis.

The ELEVATE trial was a trailblazer because other advanced therapies are starting to follow. For example, the POLARIS trial of the S1P receptor modulator ozanimod (Zeposia, Bristol Myers Squibb) has also enrolled patients with ulcerative proctitis. Additionally, there are several other biologic trials for patients with ulcerative colitis that are enrolling patients with ulcerative proctitis. We can consider this the dawn of a new era for patients with this often very debilitating disease type.

G&H Do you have any tips for managing patients with refractory ulcerative proctitis?

MC When defining refractory disease, as in the past, the treatment algorithm is very much a step-up approach, even though conventionally providers tend to use more effective therapy for patients with more severe disease. In patients with mild to moderate disease, I would still go to conventional therapies such as rectal mesalamine and rectal corticosteroids. For patients with more refractory disease, I personally believe that tacrolimus is a great option. Alternatively, patients can be shifted to the moderate to severe pathway and be treated with systemic corticosteroids, followed by etrasimod given the ELEVATE trial data. From that point on, providers generally follow the sequence used for other forms of ulcerative colitis, including small molecules and biologics. I think everyone is in agreement that there is a very limited or no role for azathioprine in patients with ulcerative proctitis, unless used in combination with an anti–tumor necrosis factor biologic.

G&H What are the priorities of research?

MC More data are needed, especially on durability. The ELEVATE trial studied patients for up to 12 months, but obviously more extensive longitudinal data are needed. Because ulcerative proctitis patients were excluded from clinical trials for so many years, we do not know enough about the long-term natural history of this disease. We know what happens when these patients are treated. However, it is not as clear what happens if they stop treatment. A patient with mild to moderate disease who is in remission may want to stop their topical therapy of mesalamine and consider just on-demand therapy as needed. Providers often think that doing this would allow the disease to extend proximally, so they recommend that patients continue therapy even if the patients are doing well. However logical and heuristically acceptable, we are not sure whether this is truly the case, as we also do not always know which patients will experience disease extension above the rectum and why. This is probably the largest knowledge gap, knowing whether treating patients with ulcerative proctitis to the target of endoscopic or histologic remission truly prevents disease extension, which otherwise occurs in 30% to 40% of these patients.

Disclosures

Dr Chiorean has done consulting and advising for Johnson & Johnson, Pfizer, BMS, AbbVie, Gilead, Lilly, and Celltrion; received grants from Pfizer, Johnson & Johnson, Gilead, and Novartis; and served as a speaker for AbbVie, Johnson & Johnson, Lilly, Takeda, Celltrion, and Pfizer.

Suggested Reading

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