ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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How to Approach Immune Checkpoint Inhibitor Enterocolitis

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G&H What are the similarities and differences between immune checkpoint inhibitor enterocolitis and inflammatory bowel disease in terms of etiology, clinical presentation, and endoscopic presentation?

YW These conditions have distinct etiologies. Immune checkpoint inhibitor (ICI) enterocolitis is a drug-induced inflammatory condition of the gastrointestinal (GI) tract, whereas inflammatory bowel disease (IBD) is a chronic autoimmune disorder characterized by enterocolitis. Despite these differences, the two conditions share many overlapping pathologic features and often present with similar clinical symptoms. ICI enterocolitis can closely resemble IBD on endoscopy, with findings such as ulcers, erythema, exudates, granulation tissue, and mucosal friability. Differentiating between the two conditions can be challenging, making a detailed medical history essential when formulating a differential diagnosis. Notably, ICI enterocolitis encompasses a broader spectrum of endoscopic and histologic presentations than classical IBD. For example, ICI-induced inflammation may manifest as microscopic colitis, which is distinct from IBD. In such cases, endoscopic findings are normal, but histology reveals inflammation consistent with lymphocytic or collagenous colitis. Furthermore, a subset of patients treated with ICIs may experience diarrhea despite normal endoscopic and histologic findings. In the absence of ICI therapy, this clinical picture is typically categorized as irritable bowel syndrome, a functional GI disorder defined by the lack of structural abnormalities. When ICI enterocolitis is suspected, patients are routinely evaluated with stool studies, endoscopy, and histologic examination to confirm inflammation and assess its severity. These objective findings are critical for guiding appropriate treatment decisions.

G&H Can patients with a history of IBD be treated with immunotherapy?

YW Yes, although there is a significantly increased risk of colitis flare-up. In a multicenter study that my colleagues and I conducted with collaborators, we found that the flare-up rate among patients with preexisting IBD receiving ICIs can be as high as 42%—even with programmed death 1/programmed death ligand 1 (PD-1/PD-L1) monotherapy, which is typically considered a lower-risk regimen. In contrast, PD-1/PD-L1 monotherapy causes enterocolitis in approximately 15% of patients without underlying IBD. Most flare-ups in this setting were clinically severe, often requiring hospitalization, aggressive immunosuppressive treatment (eg, biologic agents), and frequently leading to interruptions in cancer therapy. The etiology of these flare-ups is often difficult to distinguish—whether they are driven by ICI-induced inflammation, underlying IBD, or a combination of both remains unclear in many cases. Despite these challenges, the oncologic outcomes remain comparable: patients with IBD who receive ICIs demonstrate cancer response rates equivalent to those of non-IBD patients. Therefore, optimizing IBD at baseline is essential to reduce the risk of flare-ups and support a successful cancer treatment course.

G&H Can immunotherapy be continued in the setting of ICI enterocolitis?

YW Yes, it can. Over the past decade, both clinical experience and research have significantly advanced our understanding in this field. Initially, treatment strategies were limited, and ICI enterocolitis often disrupted cancer care, negatively impacting oncologic outcomes. However, in the current era, timely and appropriate management of colitis can lead to rapid remission. With this approach, immunosuppressive therapy can be safely continued while resuming ICI treatment long term, with excellent success in preventing colitis recurrence. Moreover, emerging research has demonstrated that fecal microbiota transplantation (FMT) offers a promising therapeutic option. FMT has been shown to induce sustained long-term remission of colitis, even during ongoing ICI therapy, lasting over a year in some cases. This novel approach is fast-acting, effective, and safe, representing an important advancement in the management of ICI-induced colitis.

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G&H How effective and safe is medical therapy for the treatment of this condition?

YW Overall, medical treatments are highly effective in managing ICI enterocolitis. Corticosteroids achieve a clinical response in approximately 60% of cases, whereas biologic agents such as infliximab and vedolizumab (Entyvio, Takeda) have demonstrated efficacy rates of around 85%. As a result, these therapies are commonly used in patients with moderate to severe ICI enterocolitis. In the short term, these therapies are generally considered safe and effective. However, the safety profile of corticosteroids warrants caution, particularly in oncology patients. Prolonged corticosteroid use is associated with increased risks of infection, hyperglycemia, osteoporosis and fractures, impaired wound healing, and potentially adverse effects on cancer outcomes and overall survival. These concerns are especially relevant in vulnerable cancer populations, making it critical to minimize corticosteroid duration whenever feasible.

Biologic agents offer a more favorable short- and long-term safety profile compared with corticosteroids, as evidenced by data from noncancer populations. Nevertheless, their safety and impact on cancer outcomes have not been thoroughly evaluated in cancer patients. Given the theoretical concern that immunosuppressive therapies may counteract the mechanism of action of ICIs, there is ongoing uncertainty regarding their long-term safety in terms of cancer progression and survival. Further research is needed to better define these risks and guide optimal treatment strategies.

G&H Could you expand on the role of FMT in this setting?

YW In 2017, our group was the first to investigate FMT as a novel treatment for ICI enterocolitis. We have continued this work over the past 8 years through two prospective clinical trials. Our data have consistently demonstrated high efficacy rates of 80% to 85%, with a favorable safety profile—both as salvage therapy in refractory cases and as frontline treatment in treatment-naive patients. Currently, owing to protocol limitations, we enroll only patients with moderate to severe colitis, defined as Common Terminology Criteria for Adverse Events grade 2 or higher. However, future directions may include expanding FMT use to patients with grade 1 colitis or even prophylactically at the initiation of immunotherapy, with the goal of reducing toxicity risk and potentially improving long-term cancer outcomes.

G&H Have there been any concerns or limitations regarding this approach?

YW There have been ongoing concerns and misconceptions regarding the safety of FMT, particularly in immunocompromised patients. Misinformation has led to the belief that FMT may increase the risk of infections or negatively impact certain medical conditions. However, scientific data to date consistently support that FMT is extremely safe when administered to appropriately selected patients. That being said, FMT is not suitable for all cancer or immunocompromised patients without careful evaluation. One of the most critical safety considerations is ensuring that patients are not neutropenic at the time of treatment, as neutropenia is a major risk factor for serious infections following FMT. In contrast, patients receiving immunosuppressive therapies—such as corticosteroids or biologic agents—can still safely undergo FMT, provided they meet other clinical criteria.

Equally important is the rigorous screening of donor stool, in accordance with US Food and Drug Administration regulations, to ensure safety and minimize the risk of transmissible infections. Close monitoring is

essential after FMT to detect any potential complications or short- and long-term adverse events. To date, I have treated nearly 200 patients across various indications and have not observed a single serious adverse event related to FMT. In my opinion, FMT is among the safest and most effective treatment options available for managing ICI enterocolitis, particularly when compared with other commonly used immunosuppressive therapies.

G&H If stopped, can ICI therapy be restarted after resolution of ICI enterocolitis, and how can recurrence be best controlled?

YW Yes, ICI therapy can be safely restarted after the resolution of colitis, as supported by data from our multicenter study. The overall recurrence rate of colitis upon ICI rechallenge is approximately 35%. However, therapies involving cytotoxic T-lymphocyte–associated antigen 4 agents carry a significantly higher recurrence risk, reaching up to 80%. Importantly, the use of concurrent immunosuppressive therapy during ICI rechallenge has been shown to reduce the recurrence rate to approximately 15%. This approach has emerged as a new standard of care, enabling more successful long-term maintenance of immunotherapy in patients who have previously experienced ICI enterocolitis. These recommendations are supported by multicenter data published in 2023 by Memorial Sloan Kettering, Massachusetts General Hospital, and MD Anderson Cancer Center, which demonstrated the effectiveness of proactive management strategies in preventing colitis recurrence.

G&H Are there any other similarities or differences between ICI enterocolitis and IBD that you would like to discuss?

YW The disease course of ICI enterocolitis differs significantly from that of IBD. IBD is a chronic, lifelong condition, whereas ICI enterocolitis is typically transient, with a duration of approximately 3 to 6 months. In many cases, complete remission can be achieved within this time frame, particularly when the inciting agent—immunotherapy—is discontinued. Once patients are off ICI therapy, their risk of recurrent colitis is often reduced. However, rare but notable cases have shown that enterocolitis can persist for years, even after the cessation of immunotherapy. These outliers have challenged our understanding of ICI-related toxicity and highlight the need for further research into the underlying mechanisms driving chronicity in such cases.

G&H What are the priorities of research?

YW The top priority in this field is to identify safer and more effective treatments—ideally those that are GI-specific, preserve overall patient health, and potentially enhance cancer outcomes. A key goal for both clinicians and patients should be to minimize reliance on systemic immunosuppression whenever possible. Exciting progress has emerged from microbiome research in recent years. Studies involving stool from cancer survivors combined with immunotherapy have shown promising results, including the restoration of cancer responses in patients with previously refractory disease—outcomes that were not seen with immunotherapy alone. Earlier this year, NBC News featured a remarkable case from MD Anderson in which a patient achieved complete remission from small bowel cancer after receiving a combination of FMT and PD-1 inhibitor therapy. I am proud to have been part of the research team that delivered FMT for this patient. This case underscores the transformative potential of microbiome-based strategies and highlights opportunities to rethink our therapeutic approaches for maximizing patient benefit.

At the same time, substantial knowledge gaps remain in the field of immunotherapy toxicity, and many important clinical questions are yet to be answered. I am hopeful that continued high-quality research within our community will drive innovation, close these gaps, and help us overcome the ongoing challenges in managing immunotherapy-related adverse events.

Disclosures

Dr Wang has served in a consultant role for Thornhill, Janssen, Alimentiv, BioNTech, Sorriso, and BeOne Medicines and has received research funding from 3-D Matrix and Janssen.

Suggested Reading

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