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A Practical Approach to Managing Immune Checkpoint Inhibitor-Induced Colitis


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INTRODUCTION

As indications for immune checkpoint inhibitors (ICIs) expand, it is critical that gastroenterologists and primary care physicians be aware of how to identify and manage associated side effects. ICIs have dramatically altered the treatment landscape and outcomes for a wide variety of cancers since they were were first approved by the Food and Drug Administration (FDA) a decade ago. ICIs are monoclonal antibodies that augment the anti-tumor immune response by blocking the immune checkpoints cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1) or its ligand PD-L1. Initially approved for the treatment of advanced melanoma, their mechanism of action targets a fundamental aspect of tumor immunology, leading to FDA approval in multiple other tumors (particularly for anti-PD-1/PD-L1).[1–6] While ICIs are effective, the resulting immune activation can lead to immune-mediated tissue damage in multiple organs. This review will cover the practical aspects of diagnosing and managing patients with ICI-induced diarrhea and colitis.

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Immune Checkpoint Inhibitors, Adverse Events and Colitis

Immune self-tolerance is regulated in part by "immune checkpoints" that restrict exaggerated immune responses and prevent autoimmune disease. Immune checkpoint inhibitors (ICIs) inhibit these immune checkpoints and allow tumor infiltrating lymphocytes to target malignant cells. There are two major classes of ICIs targeting distinct priming and effector phases of the immune response, anti-CTLA-4 and anti-PD-1/PD-L1.[1–6] In current oncologic practice, anti-PD-1/PD-L1 constitute the majority of approved tumor types for ICIs, and anti-CTLA-4 is approved as combination therapy with anti-PD-1/PD-L1 only in specific indications.[1–6]

While ICIs have revolutionized cancer treatment, the inhibition of checkpoint proteins can lead to immune-related adverse events (irAEs). IrAEs are thought to result from autoreactive

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T-cells disinhibited from attacking normal host cells. IrAEs can target multiple organs, and the gastrointestinal (GI) tract can be the target of severe or life-threatening events.[4,5] Diarrhea is the most commonly reported gastrointestinal symptom of ICIs, occurring in 30-60% of patients.[7] In oncologic practice, ICI-induced colitis is often defined clinically by symptoms of diarrhea without an infectious cause, as well as abdominal pain, mucus, tenesmus, hematochezia, or fever.[8] In general, anti-CTLA-4 is associated with earlier-onset and more severe irAEs than PD-1/PD-L1 inhibitors, and the combination increases the incidence and severity further still.[9–11] Interestingly, patients who experience an irAE of any organ system have improved overall survival compared to those without irAEs, with a specific survival benefit for GI-related irAEs.[12] Data from advanced melanoma showed that patients who discontinued ICIs due to treatment-related adverse events had similar overall survival at five years compared to the overall population.[1] Taken together, this implies that irAEs like ICI-induced colitis, if tolerable and responsive to treatment, are not necessarily associated with worse survival, and may in some circumstances correlate with more robust antitumor activity and a higher likelihood of favorable treatment response.

Initial Evaluation of Patients with ICI-Induced Diarrhea and Colitis

Evaluation and management of these patients have been outlined by multiple clinical practice updates, guidelines, and recommendations based on expert opinion and retrospective studies.[13–19] The diagnosis of ICI-induced colitis should be considered in any patient with diarrhea and colitis symptoms occurring after ICI-initiation. ICI-induced colitis occurs with a median onset of 5-7 weeks after ICI initiation, though it can start as early as one week or over six months later.[1]

The first step in evaluation is to assess severity and rule out infectious causes, including Clostridiodies difficile (C.Diff) and common bacterial, viral, and parasitic pathogens. Lactoferrin and fecal calprotectin have been studied in ICI-induced colitis as non-invasive markers to help differentiate between inflammatory versus non-inflammatory diarrhea.[20,21] Routine labs including complete blood count, complete metabolic panel, sedimentation rate, and C-reactive protein are recommended, although their diagnostic and prognostic utility are less clear in this setting than in inflammatory bowel disease (IBD). Testing for non-infectious, non-inflammatory causes of diarrhea may include checking thyroid stimulating hormone to rule out hyperthyroidism, tissue transglutaminase (TTG)-IgA and total IgA to rule out celiac disease, and lipase and fecal elastase to rule out pancreatic insufficiency, since all have been described as rare irAEs.[22] For patients with grade ≥ 2 disease who may require biologics, it is important to check for latent tuberculosis, viral hepatitis (A, B and C) and HIV. Computed tomography (CT) scans are not routinely recommended, but if there is concern for perforation or other acute pathology then a contrast-enhanced CT scan is a fast and highly informative test.[13-20]

Endoscopy with biopsy remains the gold standard for the diagnosis and risk-stratification of patients with suspected moderate-to-severe ICI-induced colitis. Patients with mild ICI-induced colitis may be diagnosed and treated empirically without endoscopic evaluation, especially if the non-invasive evaluation suggests a mild inflammatory non-infectious colitis (i.e., elevated fecal calprotectin and negative infectious stool studies). Endoscopic evaluation serves several purposes. First, the recommendations for moderate-to-severe ICI-induced colitis involve holding immunotherapy and treating with prednisone, interventions which could unnecessarily harm patients with alternative etiologies of diarrhea. Moreover, the presence of CMV or other infectious colitis can be assessed with higher sensitivity and specificity on histology. Finally, endoscopic evaluation aids in risk stratification. High-risk features such as large ulcers >1cm, deep ulcers, and pancolitis are associated with steroid treatment failure, identifying patients who would benefit from early induction with biologics.[20,23,24] ICI-induced intestinal inflammation can affect any part of the GI tract, so upper endoscopy and colonoscopy are ideal. However, retrospective studies have demonstrated that >98% of patients with ICI-induced colitis had involvement of the left (distal) colon, supporting a practice of flexible sigmoidoscopy for expedited initial evaluation.[25,26]

In select patients with a negative sigmoidoscopy or persistent or refractory symptoms, subsequent upper endoscopy and colonoscopy could be considered to look for more proximal colitis, gastritis, or enteritis.

ICI-induced colitis can be confirmed by histology. Common features include neutrophilic cryptitis, crypt abscesses, epithelial apoptosis, and increased intraepithelial lymphocytes. Anti-PD-1 is more likely than anti-CTLA-4 to exhibit features of lymphocytic or collagenous colitis, with some reports of chronic mucosal injury.[27,28] Given the possibility of microscopic colitis, it is important to perform biopsies in multiple colonic segments even if the mucosa appears endoscopically normal.

Management of ICI-Induced Diarrhea and Colitis Based on Severity

Grade 1

Grade 1 diarrhea is defined as <4 daily stools above the patient's baseline or mildly increased ostomy output, while grade 1 colitis is asymptomatic.[8] Most society practice guidelines do not recommend GI consultation for grade 1 symptoms, although fecal calprotectin and infectious stool studies should be obtained in patients with symptoms lasting for 3 days.[19] Patients with grade 1 diarrhea should be monitored closely because they may quickly progress to higher grades of diarrhea and colitis. ICIs may be held but are usually continued for mild grade 1 ICI-induced colitis.[13–19] Treatment is supportive and may include loperamide and hydration, although we typically rule out infections like *C.Diff* before prescribing anti-diarrheal agents. If the patient's symptoms do not improve after 3-14 days of conservative management, it is recommended to start enteric budesonide at 9mg per day for four weeks followed by a taper by 3mg every two weeks.[13,18] If patients do not respond to budesonide, they should be escalated to systemic steroids with prednisone 1mg/kg per grade 2 management.[13,14,16]

Grade 2

Grade 2 diarrhea is defined as 4-6 stools over baseline, or moderately increased ostomy output, while grade 2 colitis is defined by abdominal pain, mucus and hematochezia.[8] At this stage, ICIs are held, and GI should be consulted with consideration for flexible sigmoidoscopy in addition to non-invasive testing outlined above. Patients with grade 2 diarrhea and colitis are treated with prednisone 1mg/kg, followed by a taper over 4-8 weeks.[13,18] If patients do not respond within three days of starting oral prednisone, they should be escalated to IV methylprednisolone or a biologic, either infliximab (IFX) or vedolizumab (VDZ). If patients fail to respond to IV steroids within three days, then they should be treated with a biologic. Some Grade 2 patients may respond to a single dose of a biologic followed by a steroid taper, but some may require additional induction doses.[13]

Grade 3 or 4

Grade 3 diarrhea is defined as ≥ 7 stools above baseline or severe increase in ostomy output, while grade 3 colitis is defined by severe pain, fever, or peritoneal signs requiring intervention, or interference with activities of daily living.[8] Grade 4 diarrhea and colitis are defined by all the criteria of grade 3 but are also life-threatening.[8] Most grade 3 and all grade 4 patients should be hospitalized with GI consultation, and ICIs are held. The laboratory evaluation is outlined above, including necessary tests in anticipation of biologic therapy. If there is concern for perforation or other acute pathology, a contrast-enhanced CT scan should be obtained. Patients should undergo endoscopic evaluation to assess for high-risk features. Hospitalized grade 3/4 patients are started on IV methylprednisolone 1-2mg/kg. If they fail to respond to IV steroids within 72h then they should start a biologic. Patients with grade 3/4 disease will typically require three doses of IFX or VDZ, often dosed at 0, 2, and 6 weeks.[13,29,30]

For grade ≥ 2 ICI-induced colitis, ICIs are held at least until patients recover and successfully taper down to a prednisone dose of ≤10mg/day.[13,14,18] Repeat endoscopy is beneficial for patients with persistent symptoms, but also for risk stratifying patients who are being considered for restarting ICIs after recovering from ICI-induced colitis. While most experts recommend considering permanent discontinuation of anti-CTLA-4 for grade ≥ 2 ICI-induced colitis,[13,14,18] the risks and benefits should be weighed in conjunction with the treating oncologist. PD-1/PD-L1 inhibitors are generally associated with milder ICI-induced colitis

and may be restarted if patients successfully wean to ≤10mg of prednisone daily.[13–16,18] Concurrent administration of maintenance IFX while resuming ICIs was reported to prevent recurrent ICI-induced colitis in a small number of patients.[13,31] Therefore, treatment with IFX, or by extension VDZ, may allow ICIs to be restarted in some patients with prior ICI-induced colitis.

Evidence Supporting Various Therapies for Treating ICI-Induced Colitis

Glucocorticoids are the mainstay of treatment for patients with grade ≥2 ICI-induced colitis. A systematic review and meta-analysis of 1210 patients found that corticosteroids were effective in 59%.[32] Several studies have identified endoscopic features associated with steroid-refractory disease, including large >1cm ulcers, deep ulcers, pancolitis, and high colitis severity scores.[20,23,24] Therefore, in moderate cases without high-risk features, steroids are typically first-line. Enteric budesonide was not more effective than placebo in a randomized controlled trial for primary prophylaxis against anti-CTLA-4 induced colitis[33] but is effective for patients who have features of microscopic colitis on histology or patients with persistent mild grade 1 diarrhea.[13]

The anti-tumor necrosis factor (TNF) IFX is one of the most commonly prescribed agents for IBD and the best characterized biologic for treating ICI-induced colitis. While it is generally safe and well-tolerated, relative contraindications include active or recurrent infections, untreated tuberculosis or HBV, moderate-to-severe heart failure, or demyelinating conditions. With regard to the risk of malignancy with anti-TNF agents, a recent meta-analysis found that the risk of new cancer or cancer recurrence in patients with a history of cancer was similar to non-biologic therapies.[34] The risk may be even lower in ICI-induced colitis patients who commonly receive limited induction doses rather than long-term anti-TNF maintenance therapy. IFX appears to be effective in approximately 80% of steroid-refractory patients.[24,32] There are mixed data regarding whether IFX treatment affects the efficacy of ICIs by interfering with the anti-tumor immune response. One retrospective study found similar overall survival in patients treated with the combination of steroids and IFX versus steroids alone,[12] while another retrospective study reported that patients treated with IFX and steroids exhibited reduced overall survival compared to steroids alone.[35] Nevertheless, IFX appears to be generally safe and effective in this setting.

VDZ is another option for patients with steroid- or IFX-refractory disease. VDZ targets the integrin $\alpha_4\beta_7$ and inhibits lymphocyte trafficking to the gut with a favorable safety profile. VDZ has been used effectively in steroid and IFX non-responders, but the response rates may be lower in IFX non-responders as these patients likely represent a more refractory population.[30] VDZ therefore is an option as both a first-line biologic in steroid-refractory patients as well as rescue therapy for IFX non-responders.

IFX and VDZ have not been compared head-to-head, so choosing between the two can depend on several factors. One retrospective cohort study suggested that patients who received VDZ for ICI-induced colitis had a shorter steroid course, shorter hospital stay, and lower recurrence of diarrhea or colitis compared to patients treated with IFX, although it is unclear if the VDZ-treated patients had less severe disease.[36] Extrapolating from IBD, IFX is more effective than VDZ for moderate-to-severe disease, but VDZ is associated with fewer infectious complications.[37,38] VDZ also induces a response more slowly than IFX in ICI-induced colitis, with a median response time of five days for VDZ versus two days for IFX.[24,30] Given these data, our general practice is to use IFX for hospitalized patients with more severe ICI-induced colitis, and VDZ for more moderate patients, patients with relative contraindications to anti-TNF therapy, or if we anticipate needing a maintenance biologic. Given its favorable side-effect profile, VDZ may have a role for secondary prophylaxis, though more data are needed. Regardless of the agent used, prompt evaluation, diagnosis, and initiation

of treatment are critical. In a retrospective study, patients treated with a biologic within 10 days from onset of symptoms were found to have shorter duration of symptoms, fewer hospitalizations, and were weaned off of steroids more easily than patients treated 10 days after symptom-onset.[39]

Remaining Questions in Clinical Practice

As the indication for ICIs are expanding, there are many questions remaining on how to manage ICI-induced colitis. For example, when and how to safely restart ICI therapy in patients who have recovered from ICI-induced colitis requires further investigation. Treating to complete mucosal healing,[40] or concomitant administration of a biologic may reduce the risk of recurrent ICI-induced colitis, but we need more studies to determine the best approach.

Beyond IFX and VDZ, data supporting other therapies are generally limited to small case series and case reports. Tofacitinib (JAK inhibitor), ustekinumab (anti-IL-12/23), and fecal microbial transplant have been described as effective in small numbers of patients who had failed steroids, IFX, and VDZ.[41–45] It will be helpful to have additional data regarding how best to prioritize biologics or other treatments for refractory patients. As we learn more about the underlying microbial, immunologic, and molecular mechanisms of ICI-induced colitis, it would be ideal to identify biomarkers of patients at highest risk for severe disease and initiate primary prophylaxis.[46–49] Patients with pre-existing IBD appear to be at increased risk of developing GI irAE compared to patients without IBD.[49] Given that patients with IBD respond well to ICIs,[50–52] immunotherapy should not be withheld,[13,16] but it will be important to determine how best to optimize control of their IBD prior to immunotherapy initiation to prevent treatment-related complications.

In conclusion, ICIs have dramatically altered the treatment of many cancers and have brought hope to many patients. By virtue of their mechanism, ICIs lead to a variety of side-effects that may portend improved efficacy against their underlying malignancy. With close monitoring, prompt diagnosis, appropriate treatment, and multidisciplinary collaboration, the associated adverse effects can generally be managed effectively. ■

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