Diagnosis and Management of Immune Checkpoint Inhibitor Colitis

Jana G. Hashash, MD, MSc,[1,2] Fadi F. Francis, MD,[2] and Francis A. Farraye, MD, MSc[1]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Florida

[2]Division of Gastroenterology and Hepatology, American University of Beirut, Beirut, Lebanon

Corresponding author:
Dr Jana G. Hashash
Division of Gastroenterology and Hepatology
Inflammatory Bowel Disease Center
Mayo Clinic
4500 San Pablo Road S
Jacksonville, FL 32224
Tel: (904) 953-0729
Fax: (904) 953-6225
E-mail: AlHashash.Jana@mayo.edu

Abstract: Increased use of immune checkpoint inhibitors (ICIs) has created a rise in immune-related adverse events (irAEs), which may affect any system in the body. Gastrointestinal (GI) irAEs such as immune-mediated colitis are common, occurring in 35% to 50% of patients receiving ICIs. GI irAEs usually develop 6 to 8 weeks after ICI initiation and can involve any part of the GI system. Patients with immune-mediated colitis are categorized into 1 of 5 grades based on the National Cancer Institute's Common Terminology Criteria for Adverse Events, which also guide treatment decisions. An infectious cause for the diarrhea should be excluded in all patients. Patients with grade 1 symptoms are managed conservatively. Patients with grade 2 or higher symptoms should undergo a colonoscopy and are treated with systemic corticosteroids and, depending on their response, biologic therapy. The aim of this article is to review the diagnosis and management of patients with immune-mediated colitis, which should be identified early and addressed promptly to avoid detrimental outcomes.

Keywords
Immune checkpoint inhibitors, immune-related adverse events, colitis, diarrhea, biologic therapy

Immunotherapies, particularly immune checkpoint inhibitors (ICIs), are effective for the treatment of a variety of malignancies, including melanoma, small cell and non–small cell lung cancer, and renal cell carcinoma.[1-4] Immune checkpoint proteins diminish the body's immune response, thereby preventing autoimmunity. These proteins include programmed death 1 (PD-1) and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and their ligands on antigen-presenting cells, programmed death ligand 1 (PD-L1) and cluster of differentiation (CD)80/CD86, respectively. Tumor cells use these checkpoint proteins to escape the immune system. ICIs target the checkpoint proteins, particularly CTLA-4, PD-1, and PD-L1, enhancing the innate immune system by promoting cytotoxic T-cell survival and augmenting tumor surveillance and antitumor effects.[5] As such, off-target inflammation and autoimmunity can occur, resulting in a number of inflammatory toxicities from ICIs referred to as immune-related adverse events (irAEs).

Ipilimumab (Yervoy, Bristol Myers Squibb), an anti–CTLA-4 antibody, was approved in 2011 for the treatment of unresectable metastatic

melanoma, with subsequent approvals for renal cell carcinoma and microsatellite instability–high cancers.[6] Pembrolizumab (Keytruda, Merck) and nivolumab (Opdivo, Bristol Myers Squibb), both approved in 2014, are anti–PD-1 agents that block the interaction between PD-1 and the ligands PD-L1 and programmed death ligand 2. These agents are approved for melanoma, metastatic non–small cell lung cancer, head and neck squamous cancers, gastric adenocarcinoma, urothelial cancer, and Hodgkin lymphoma.[7] Nivolumab also is approved for the treatment of hepatocellular carcinoma and renal cell carcinoma. Cemiplimab (Libtayo, Regeneron and Sanofi-Aventis) is an anti–PD-1 agent used for treating cutaneous squamous cell carcinoma.[8] Two anti–PD-L1 agents—atezolizumab (Tecentriq, Genentech) and durvalumab (Imfinzi, AstraZeneca)—are approved for the treatment of non–small cell and small cell lung cancer, urothelial cancer, and breast cancer. Avelumab (Bavencio, EMD Serono), another anti–PD-L1 agent, is used for treating Merkel cell carcinoma, urothelial cancer, and renal cell carcinoma. Table 1 provides a summary of these agents and their respective indications.

IrAEs commonly occur in patients receiving ICIs, with higher rates seen in patients receiving simultaneous combination agents. The most common irAEs are dermatologic, occurring in 44% to 68% of patients, followed by gastrointestinal (GI; 35%-50%), hepatic (5%-10%), and endocrine events (6%).[9-11] IrAEs can occur at any point after starting treatment with an ICI and even after stopping the medication.[12-14] IrAEs are the most common reason for ICI therapy discontinuation.[12-14] Compared with anti–PD-1 and anti–PD-L1 agents, anti–CTLA-4 therapies are associated with higher rates of irAEs (61%-79% vs 27%, respectively) and more severe events (17%-31% vs 6%, respectively).[10,15] Development of irAEs is dose-dependent with anti–CTLA-4 agents, but not with anti–PD-1 and anti–PD-L1 agents.[2,6] Fatalities are highest with the use of anti–CTLA-4 agents at 1.08%, followed by 0.38% with anti–PD-L1 agents and 0.36% with anti–PD-1 therapies.[16] Most fatalities because of anti–CTLA-4 irAEs are from colitis, whereas fatalities because of anti–PD-1 and anti–PD-L1 irAEs are from pneumonitis, myocarditis, and hepatitis.[16]

Patients with melanoma have been found to develop more dermatologic and GI irAEs compared with patients with non–small cell lung cancer.[17,18] The question of whether the development of irAEs is associated with a beneficial treatment response to ICIs has been studied. Although this theory is still controversial, there are meta-analyses supporting this observation.[19-22]

GI irAEs can occur anywhere in the GI tract, including the esophagus, stomach, small bowel, colon, pancreas, gallbladder, bile ducts, and liver.[23,24] Although these events typically occur 6 to 8 weeks after ICI therapy initiation,[11,25] they can, as previously discussed, occur any time after starting ICI therapy and even months after discontinuation of the inciting drug.[11,20,25-29] Timely diagnosis of GI irAEs is crucial, as they may be life-threatening. Diarrhea occurs at a rate of 30.2% to 50% in patients

Table 1. FDA-Approved Immune Checkpoint Inhibitors

Class and Generic Name	Year of Approval	Indication(s)
Anti–CTLA-4		
Ipilimumab	2011	• Melanoma • Renal cell carcinoma • Microsatellite instability–high cancers
Anti–PD-1		
Pembrolizumab	2014	• Melanoma • Metastatic NSCLC • Head and neck squamous cancers • Gastric adenocarcinoma • Urothelial cancer • Hodgkin lymphoma • Mismatch repair–deficient solid tumors
Nivolumab	2014	• Melanoma • Metastatic NSCLC • Head and neck squamous cancers • Gastric adenocarcinoma • Urothelial cancer • Hodgkin lymphoma • Hepatocellular carcinoma • Renal cell carcinoma
Cemiplimab	2018	• Cutaneous squamous cell carcinoma
Anti–PD-L1		
Atezolizumab	2016	• NSCLC • Small cell lung cancer • Urothelial cancer • Breast cancer (triple negative)
Durvalumab	2017	• NSCLC (stage 3) • Small cell lung cancer • Urothelial cancer • Breast cancer
Avelumab	2017	• Merkel cell carcinoma • Urothelial cancer • Renal cell carcinoma

CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; FDA, US Food and Drug Administration; NSCLC, non–small cell lung cancer; PD-1, programmed death 1; PD-L1, programmed death ligand 1.

Table 2. Common Terminology Criteria for Adverse Events[42]

Grade	Diarrhea	Colitis
1	Increase of stool frequency <4/day over baseline; mild increase in ostomy output compared with baseline	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Increase of stool frequency 4-6/day over baseline; moderate increase in ostomy output compared with baseline	Abdominal pain; mucus or blood in stool
3	Increase of stool frequency ≥7/day over baseline, incontinence, need for hospitalization, and limiting self-care activity of daily living; severe increase in ostomy output compared with baseline	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs
4	Life-threatening consequences; urgent need for intervention	Life-threatening consequences; urgent intervention indicated
5	Death	Death

receiving anti–CTLA-4 agents and 12.1% to 13.7% in patients receiving anti–PD-1 agents, whereas the incidence of colitis ranges from 5.7% to 22% in patients on anti–CTLA-4 agents and 0.7% to 1.6% in patients on anti–PD-1 agents.[30-37]

The aim of this article is to review the diagnosis and management of immune-mediated colitis. Although most patients with immune-mediated complications are primarily cared for by oncologists, gastroenterologists play an important role in the diagnosis, risk stratification, and management of these patients.

Clinical Presentation of Immune Checkpoint Inhibitor Colitis

Clinicians should have a high index of suspicion for immune-mediated colitis when evaluating oncology patients receiving ICIs who present with diarrhea. Prompt diagnosis is critical because the diarrhea and abdominal pain may quickly develop into ileus, toxic megacolon, bowel perforation, and death. This rapid progression is most commonly seen in patients treated with the anti–CTLA-4 agent ipilimumab.[38-41] Currently, the National Cancer Institute categorizes patients with immune-mediated colitis into 1 of 5 grades based on the Common Terminology Criteria for Adverse Events (CTCAE), which solely rely on symptoms (Table 2).[42]

Diagnostic Workup of Immune Checkpoint Inhibitor Colitis

Patients should undergo a detailed history and a complete physical examination. Clinicians should use the CTCAE scoring system to categorize their patient's grade, as this dictates workup and treatment. Infectious causes of the diarrhea should be excluded in patients receiving ICIs despite the low prevalence of these causes (5%).[38] Stool studies, including *Clostridioides difficile* and stool culture, should be obtained, especially in patients with grade 2 or higher immune-mediated colitis.[38] Ova and parasite tests are usually obtained in patients with risk factors and are based on local prevalence.[38] Although immune-mediated pancreatic insufficiency is uncommon, fecal pancreatic elastase also should be obtained to rule out exocrine pancreatic insufficiency, especially in patients with steatorrhea or in those whose disease has failed to respond to initial treatments.[8,43] In a recent clinical practice update, the American Gastroenterological Association (AGA) advised early stool testing for the inflammatory markers lactoferrin and/or calprotectin in patients with grade 2 or higher colitis and selected patients with less-severe diarrhea in order to stratify patients for endoscopic evaluation.[38] Despite their low specificity, blood tests, including a complete blood count, erythrocyte sedimentation rate, and C-reactive protein, are usually ordered in addition to a complete metabolic panel, albumin, and thyroid-stimulating hormone. It is also recommended to check tissue transglutaminase immunoglobulin A (IgA) and total IgA to exclude new-onset celiac disease, which is a rare complication of ICIs.[44,45] Clinicians also should test for hepatitis B infection and latent tuberculosis early on in case a biologic treatment is urgently needed.[24] The AGA also recommends checking serology for HIV and hepatitis C virus infection.[38] Table 3 provides the diagnostic workup for patients with ICI colitis.[46]

Endoscopic Evaluation of Immune Checkpoint Inhibitor Colitis

It is important to recognize that endoscopic findings do not always correlate with clinical symptoms.[22,47,48]

Table 3. Diagnostic Workup of Patients With Gastrointestinal Immune-Related Adverse Events[46]

Stool Testing
• *Clostridioides difficile*, culture • Ova/parasites (risk factors, local prevalence) • Pancreatic elastase • Inflammatory markers (lactoferrin and/or calprotectin)
Blood Work
• Complete blood count • Complete metabolic panel • Thyroid-stimulating hormone • Inflammatory markers (CRP, ESR) • Celiac panel (tissue transglutaminase IgA and total IgA) • HIV
Prebiologic Workup
• Hepatitis B surface antibody, hepatitis B surface antigen, hepatitis B core antibody (IgG or total) • Hepatitis C antibody • Interferon-gamma release assay • Chest radiograph
Endoscopic Evaluation
• Colonoscopy or flexible sigmoidoscopy (in grade ≥2 per CTCAE or in all patients if following BSG guidelines)

BSG, British Society of Gastroenterology; CRP, C-reactive protein; CTCAE, Common Terminology Criteria for Adverse Events; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin.

Regardless, early endoscopy and tissue biopsies are the gold standards for diagnosing immune-mediated colitis, assessing disease severity, and risk-stratifying patients to guide further therapy in a timely manner. Although the British Society of Gastroenterology (BSG) recommends performing a colonoscopy on all patients with GI irAEs, the AGA reserves endoscopic evaluation for patients with grade 2 or higher GI irAEs.[22,24,26,49] Endoscopy should be considered before initiation of high-dose systemic glucocorticoids, in patients with corticosteroid-refractory disease, and in those previously exposed to immunosuppressants to exclude the presence of opportunistic infections.[22,24,26,38,49] Because 98% of GI irAEs involve the left colon, a flexible sigmoidoscopy rather than a full ileocolonoscopy can be performed in most cases.[50-52]

Endoscopic findings are nonspecific, and they can demonstrate normal mucosa, mucosal edema, erythema, erosions, loss of vascular pattern, and superficial or deep mucosal ulcerations, either in a patchy or continuous fashion (Figure 1).[22,47,53] The presence of deep, large ulcers is a high-risk feature and associated with increased need for biologic therapy, increased need for hospitalization, and longer hospital stays.[54] Colonic ulcers are the only identifiable predictor of response to treatment and need for biologic therapy.[22,48] Endoscopic inflammation severity in immune-mediated colitis can be characterized using MD Anderson Cancer Center Endoscopic Inflammation Grading and the Mayo Endoscopic Score. MD Anderson Cancer Center Endoscopic Inflammation Grading categorizes patients into (1) mild severity: normal endoscopy and normal histology; (2) moderate severity: normal colon appearance with pathology showing inflammation; small ulcer less than 1 cm, shallow ulcer less than 2 mm, and/or number of ulcers less than 3; or inflammation limited to the left colon only, nonulcer formation; and (3) high severity: large ulcer greater than or equal to 1 cm, deep ulcer greater than or equal to 2 mm, and/or number of ulcers greater than or equal to 3; or extensive inflammation beyond the left colon. As for the Mayo Endoscopic Score, patients are categorized into 4 groups based on their disease activity: (1) score 0, which reflects normal or inactive disease activity and no abnormal endoscopic features; (2) score 1, which reflects mild disease activity and endoscopic evidence of erythema and/or decreased vascular pattern; (3) score 2, which reflects moderate disease activity and endoscopic features of marked erythema, absent vascular pattern, friability, and erosions; and (4) score 3, which reflects severe disease activity and endoscopic evidence of ulcerations and spontaneous bleeding.

Up to 37% of patients with immune-mediated colitis have a normal colonoscopy, and 15% of these patients also have normal biopsies.[22,54] Even endoscopically normal mucosa should be biopsied to exclude microscopic inflammation because 90% of patients with grade 1 colitis have histologic changes.[22,55] In some situations, follow-up endoscopy is important to monitor response to therapy and determine the appropriate time to resume ICIs.[24] Alternatively, recent evidence has demonstrated that fecal calprotectin is strongly associated with endoscopic severity in patients with immune-mediated colitis and may serve as a useful noninvasive marker of endoscopic and histologic remission.[54,56] Prospective data are needed to confirm whether fecal calprotectin can be used in the treatment choice of patients and to stratify their need for further endoscopic evaluation.

Histologic features of immune-mediated colitis vary and may show changes of acute colitis, chronic colitis, acute and chronic colitis, or microscopic colitis. The majority of patients have acute inflammatory changes on biopsy with infiltration of the lamina propria with neutrophils, lymphocytes, plasma cells, and eosinophils. In almost 50% of patients, chronic inflammation with submucosal infiltration is identified at presentation.[22,57,58] In patients with anti–PD-1–induced colitis, histology usually demonstrates active colitis with crypt neutrophil infiltration, crypt distortion, and pronounced epithelial reactive changes. In contrast, patients with anti–CTLA-4–induced colitis frequently demonstrate lymphocytic,

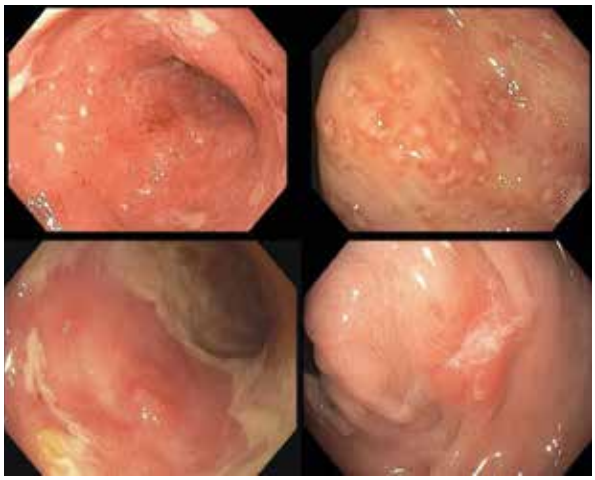

Figure 1. Endoscopic appearance of immune-mediated colitis.

plasma cell, and eosinophilic infiltration of the lamina propria. Granulomas also have been rarely reported.[51] In the majority of cases, the inflammatory involvement is diffuse in nature.[59]

Findings on cross-sectional abdominal imaging are nonspecific and include bowel wall thickening, colon distention, and mesenteric vessel congestion. Cross-sectional imaging should be performed when there is a suspicion of complications from the colitis such as toxic megacolon, perforation, obstruction, or abscess.[8] Such patients usually display symptoms of abdominal pain, fever, or bleeding.

Management of Immune Checkpoint Inhibitor Colitis

Multiple oncology and gastroenterology societies have developed practice and management guidelines for immune-mediated colitis.[14,60-62] These recommendations are based on retrospective analyses and expert opinions owing to the paucity of prospective data on the management of immune-mediated colitis. Treatment goals are the rapid reversal of symptoms, the avoidance of complications, and, when possible, enabling the continuation or reintroduction of immunotherapy.[62]

Although CTCAE grading is not predictive of treatment response or the need for secondary immune suppression, most treatment guidelines recommend therapies based on CTCAE colitis grades. However, the treatment algorithm proposed by the AGA Clinical Practice Update on Diagnosis and Management of Immune Checkpoint Inhibitor Colitis goes further by combining CTCAE grading with endoscopic inflammation severity scoring, specifically in patients with grade 2 or higher colitis.[38,63] As previously discussed, the presence of colonic ulcers is the only identified predictor of treatment response and need for secondary immune suppression.[22]

Supportive care is recommended for patients with grade 1 colitis (Figure 2). These patients are advised to increase oral hydration and to adhere to a bland diet. ICI therapy can be continued in patients with grade 1 colitis.[38] Although most guidelines include the use of antimotility agents, these agents could theoretically mask deteriorating symptoms or precipitate toxic megacolon.[62] The BSG recommends urgent flexible sigmoidoscopy and biopsy, even in the presence of macroscopically normal mucosa, as part of the initial workup and to proceed with ileocolonoscopy in patients with treatment-refractory or persistent diarrhea, especially in patients with a normal sigmoidoscopy.[62] However, other societies reserve endoscopic evaluation (colonoscopy or flexible sigmoidoscopy) for patients with grade 2 or higher colitis. They also recommend using the stool inflammatory markers lactoferrin and/or calprotectin to risk-stratify patients with grade 1 colitis for endoscopic evaluation.[38]

For patients with grade 2 colitis, ICIs should be temporarily held until symptoms return to a grade 1 level. Consideration should be given to permanently discontinue anti–CTLA-4 agents, whereas anti–PD-1 and anti–PD-L1 agents may be restarted if patients recover to grade 1 or less.[61] Hospitalization is advised for patients with grade 2 symptoms and evidence of dehydration or systemic symptoms such as fever. Based on American Society of Clinical Oncology guidelines, patients with grade 2 colitis should be treated with corticosteroids starting at an initial dose of 1 mg/kg/day of prednisone or equivalent.[61] If symptoms fail to improve after 48 to 72 hours (although some clinicians may wait 7 days), increasing the corticosteroid dose to prednisone 2 mg/kg/day is recommended, whereas other clinicians may switch to intravenous methylprednisolone sodium succinate.[14,46,60] If symptoms improve to grade 1 or less, corticosteroids should be tapered over at least 4 to 6 weeks before resuming ICI treatment. Restarting an ICI while on low-dose corticosteroid may be considered.[61] National Comprehensive Cancer Network (NCCN) guidelines recommend starting prednisone/methylprednisolone at a dose of 1 to 2 mg/kg/day. If there is no improvement after 2 to 3 days, patients should be started on biologic therapy with infliximab or vedolizumab (Entyvio, Takeda) while continuing corticosteroids.[64] Based on the AGA Clinical Practice Update, patients with grade 2 colitis and mild endoscopic inflammation activity should be treated with mesalamine or budesonide for the management of immune-mediated microscopic colitis.[38,47] Patients who are refractory to the aforementioned regimens should be started on oral corticosteroids. If there is no symptom improvement after 3 days, intravenous corticosteroids should be initiated. It has been suggested that ICIs can be resumed in patients who achieve clinical remission

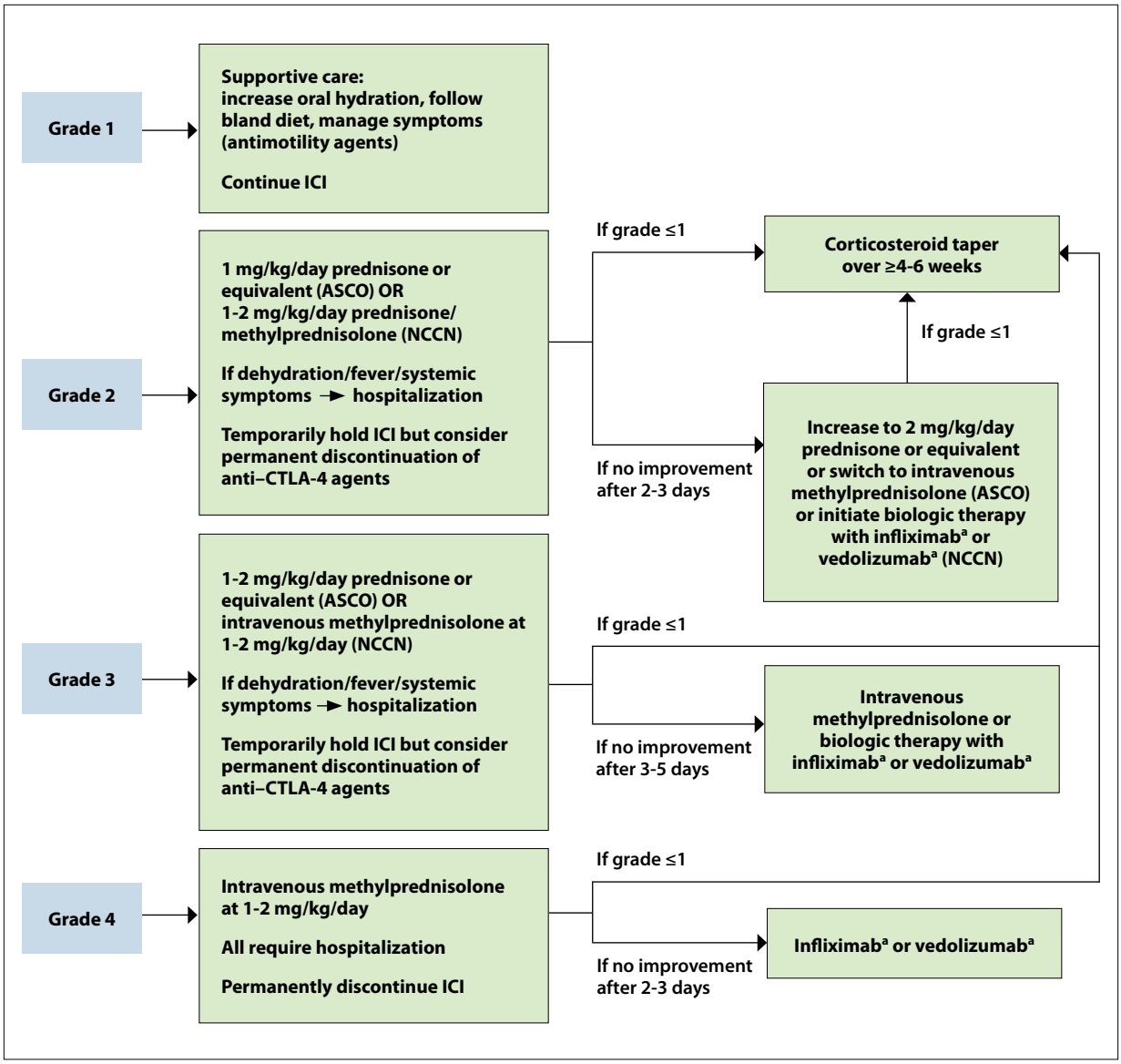

Figure 2. Management algorithm for patients with immune-mediated colitis. Adapted from Collins et al[46] and Powell et al.[62]

ASCO, American Society of Clinical Oncology; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; ICI, immune checkpoint inhibitor; NCCN, National Comprehensive Cancer Network.

[a]When biologic therapy is initiated, either infliximab or vedolizumab can be administered. Infliximab is given at a dose of 5 mg/kg at weeks 0, 2, and 6, whereas vedolizumab is given at a dose of 300 mg at weeks 0, 2, and 6.

after they complete their corticosteroid taper. However, if remission is not achieved after intravenous corticosteroids, then a single dose of infliximab or vedolizumab can be administered. If clinical remission is not maintained, patients should continue infliximab or vedolizumab and undergo a repeat colonoscopy. Only after clinical remission is achieved and corticosteroids are tapered may ICI therapy be resumed.[38,61]

Similar to patients with grade 2 colitis, for those with grade 3 colitis, consideration should be given to permanently discontinue anti–CTLA-4 agents, whereas anti–PD-1 and anti–PD-L1 agents can be restarted if patients recover to grade 1 or less. Hospitalization is advised for patients with dehydration or systemic symptoms. Corticosteroids are administered at an initial dose of 1 to 2 mg/kg/day of prednisone or equivalent. If symptoms improve to grade 1 or less, the patient should be switched to an oral prednisone taper over at least 4 to 6 weeks.[23] If symptoms persist 3 to 5 days after starting prednisone or if recurrence occurs, intravenous corticosteroids

or infliximab or vedolizumab would be the next step.[61] NCCN guidelines recommend treating patients with grade 3 colitis with intravenous methylprednisolone at 1 to 2 mg/kg/day. If there is no response after 2 to 5 days, biologic therapy with infliximab or vedolizumab should be initiated.[64]

In patients with grade 4 colitis, permanently discontinuing ICI treatment is recommended. Hospitalization is recommended for all patients with grade 4 colitis. NCCN guidelines also recommend treating patients with grade 4 colitis with intravenous methylprednisolone at 1 to 2 mg/kg/day or equivalent until symptoms improve to grade 1 or less. Corticosteroids are then tapered over at least 4 to 6 weeks. If symptoms persist after 2 to 3 days of corticosteroid treatment or if ulcers are noted during colonoscopy, prompt administration of infliximab at 5 mg/kg or vedolizumab at 300 mg should be considered.[64]

It should be noted that two-thirds of patients with immune-mediated colitis respond to corticosteroids, whereas the other one-third of patients have no or an inadequate response and need a second-line immunosuppressive agent such as infliximab or vedolizumab.[65-67]

Selection of infliximab or vedolizumab is based on patient and underlying malignancy risk factors.[38] Vedolizumab is a gut-selective $\alpha 4\beta 7$ agent and is not associated with the systemic immunosuppression seen with the tumor necrosis factor–α inhibitor infliximab. Possible adverse events from infliximab include infections, lymphoma, and nonmelanoma skin cancers. A recent multicenter, retrospective, observational cohort study of 184 patients revealed that infliximab and vedolizumab had comparable efficacy in achieving clinical remission in patients with immune-mediated colitis.[68] In addition, patients who received vedolizumab had less corticosteroid exposure, fewer hospitalizations, and shorter hospital stays, but a longer time to clinical response when compared with patients who received infliximab.[68] Lower rates of cancer progression and better overall survival rates were seen in the vedolizumab group compared with the infliximab group.[68]

Patients requiring infliximab or vedolizumab typically receive 3 induction doses (at weeks 0, 2, and 6) and do not need longer-term maintenance treatment because their response to therapy usually occurs in less than 1 week.[66,67] The dose of infliximab is 5 mg/kg, and the vedolizumab dose is the standard 300-mg dose per infusion. Patients who plan to resume ICIs may need to continue maintenance treatment with these biologic agents. Patients who do not respond to infliximab can switch to vedolizumab and vice versa.[67] For patients whose disease fails both vedolizumab and infliximab, additional options include surgery, fecal microbiota transplantation, and other pharmacologic agents such as ustekinumab (Stelara, Janssen), tofacitinib (Xeljanz, Pfizer), or abatacept (Orencia, Bristol Myers Squibb); however, these medications should be used with caution because they may interfere with antitumor response.[38,69-72]

Patients with underlying inflammatory bowel disease (IBD) are at increased risk for GI irAEs compared with non-IBD patients, but these events can be managed.[73-76] A recently published case series of 13 IBD patients, 5 with Crohn's disease and 8 with ulcerative colitis, described the impact of ICIs on patients with known IBD.[74] Of these 13 patients, 53.8% had melanoma, 61.5% were receiving pembrolizumab, and 38.5% were receiving nivolumab.[74] One of the 5 patients with Crohn's disease (not on IBD therapy) and 3 of the 8 patients with ulcerative colitis (1 of whom was on a biologic, vedolizumab) developed a flare that required corticosteroids. The time to flare occurred at a median of 5 months after the start of the ICI. In all 4 patients with IBD who had a flare after ICI initiation, there was no need to discontinue the ICI. In a retrospective study of 21 patients with IBD and 4 patients with microscopic colitis, rates of immune-mediated colitis were high, resulting in ICI discontinuation.[77] The effects of ICIs on tumor response were the same between patients with and without IBD.[73]

Prevention of Immune Checkpoint Inhibitor Colitis

To date, no effective therapies have been identified to prevent diarrhea or enterocolitis in patients treated with ICIs.[62] Two randomized, placebo-controlled trials failed to show a benefit of topical budesonide in preventing ipilimumab-induced enterocolitis.[59,78]

Recurrence of Immune Checkpoint Inhibitor Colitis

Most cases of ICI colitis will not recur unless the patient receives further ICI therapy. The decision to resume the same ICI or an alternative agent depends on the patient, the severity of immune-mediated colitis, and the underlying malignancy. Usually, resumption of the same ICI is suggested for patients who develop a less severe grade 1 colitis. Permanent discontinuation of anti–CTLA-4 therapy is recommended in patients who develop severe immune-mediated colitis.[24] The risk of recurrent immune-mediated colitis was found to be almost 30% for most regimens, but this risk was higher for patients who were switched from PD-1/PD-L1 inhibitors to CTLA-4 inhibitors.[79] If toxicity recurs after rechallenge, permanent discontinuation of that ICI class is recommended. A published case series reported that maintaining patients on infliximab or vedolizumab is effective at reducing the

risk of recurrent immune-mediated colitis in patients continuing their ICI.[80] The effect of long-term biologic therapy on tumors and response to ICIs is still unclear.

Conclusion

As ICI use increases, so will the frequency of GI irAEs. Gastroenterologists should be familiar with the prompt diagnosis and management of immune-mediated colitis, with the goal of improving symptoms, avoiding complications, and enabling resumption of antitumor treatment in a timely manner.

Disclosures

The authors have no relevant conflicts of interest to disclose.

References

1. Romano E, Kusio-Kobialka M, Foukas PG, et al. Ipilimumab-dependent cell-mediated cytotoxicity of regulatory T cells ex vivo by nonclassical monocytes in melanoma patients. *Proc Natl Acad Sci USA*. 2015;112(19):6140-6145.
2. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.
3. Ribas A, Hamid O, Daud A, et al. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. *JAMA*. 2016;315(15):1600-1609.
4. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627-1639.
5. Pauken KE, Dougan M, Rose NR, Lichtman AH, Sharpe AH. Adverse events following cancer immunotherapy: obstacles and opportunities. *Trends Immunol*. 2019;40(6):511-523.
6. Ascierto PA, Del Vecchio M, Robert C, et al. Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2017;18(5):611-622.
7. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol*. 2015;33(17):1974-1982.
8. Bellaguarda E, Hanauer S. Checkpoint inhibitor–induced colitis. *Am J Gastroenterol*. 2020;115(2):202-210.
9. Ribas A, Camacho LH, Lopez-Berestein G, et al. Antitumor activity in melanoma and anti-self responses in a phase I trial with the anti-cytotoxic T lymphocyte-associated antigen 4 monoclonal antibody CP-675,206. *J Clin Oncol*. 2005;23(35):8968-8977.
10. Bertrand A, Kostine M, Barnetche T, Truchetet M-E, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. *BMC Med*. 2015;13:211.
11. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol*. 2012;30(21):2691-2697.
12. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev*. 2016;44:51-60.
13. Schadendorf D, Wolchok JD, Hodi FS, et al. Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: a pooled analysis of randomized phase II and III trials. *J Clin Oncol*. 2017;35(34):3807-3814.
14. Haanen JBAG, Carbonnel F, Robert C, et al; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl 4):iv119-iv142.
15. Wang P-F, Chen Y, Song S-Y, et al. Immune-related adverse events associated with anti-PD-1/PD-L1 treatment for malignancies: a meta-analysis. *Front Pharmacol*. 2017;8:730.
16. Wang DY, Salem J-E, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4(12):1721-1728.
17. De Velasco G, Je Y, Bossé D, et al. Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients. *Cancer Immunol Res*. 2017;5(4):312-318.
18. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of immunotherapy for the practitioner. *J Clin Oncol*. 2015;33(18):2092-2099.
19. Teulings H-E, Limpens J, Jansen SN, et al. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. *J Clin Oncol*. 2015;33(7):773-781.
20. Wang Y, Abu-Sbeih H, Mao E, et al. Immune-checkpoint inhibitor-induced diarrhea and colitis in patients with advanced malignancies: retrospective review at MD Anderson. *J Immunother Cancer*. 2018;6(1):37.
21. Kostine M, Rouxel L, Barnetche T, et al; FHU ACRONIM. Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer-clinical aspects and relationship with tumour response: a single-centre prospective cohort study. *Ann Rheum Dis*. 2018;77(3):393-398.
22. Wang Y, Abu-Sbeih H, Mao E, et al. Endoscopic and histologic features of immune checkpoint inhibitor-related colitis. *Inflamm Bowel Dis*. 2018;24(8):1695-1705.
23. Thompson JA, Schneider BJ, Brahmer J, et al. Management of immunotherapy-related toxicities, version 1.2019. *J Natl Compr Canc Netw*. 2019;17(3):255-289.
24. Kröner PT, Mody K, Farraye FA. Immune checkpoint inhibitor-related luminal GI adverse events. *Gastrointest Endosc*. 2019;90(6):881-892.
25. Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Front Pharmacol*. 2017;8:49.
26. Geukes Foppen MH, Rozeman EA, van Wilpe S, et al. Immune checkpoint inhibition-related colitis: symptoms, endoscopic features, histology and response to management. *ESMO Open*. 2018;3(1):e000278.
27. Som A, Mandaliya R, Alsaadi D, et al. Immune checkpoint inhibitor-induced colitis: a comprehensive review. *World J Clin Cases*. 2019;7(4):405-418.
28. Yamauchi R, Araki T, Mitsuyama K, et al. The characteristics of nivolumab-induced colitis: an evaluation of three cases and a literature review. *BMC Gastroenterol*. 2018;18(1):135.
29. Marin-Acevedo JA, Chirila RM, Dronca RS. Immune checkpoint inhibitor toxicities. *Mayo Clin Proc*. 2019;94(7):1321-1329.
30. Abu-Sbeih H, Tang T, Lu Y, et al. Clinical characteristics and outcomes of immune checkpoint inhibitor-induced pancreatic injury. *J Immunother Cancer*. 2019;7(1):31.
31. Abu-Sbeih H, Tran CN, Ge PS, et al. Case series of cancer patients who developed cholecystitis related to immune checkpoint inhibitor treatment. *J Immunother Cancer*. 2019;7(1):118.
32. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med*. 2015;372(21):2006-2017.
33. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. *Ann Oncol*. 2017;28(10):2377-2385.
34. Gupta A, De Felice KM, Loftus EV Jr, Khanna S. Systematic review: colitis associated with anti-CTLA-4 therapy. *Aliment Pharmacol Ther*. 2015;42(4):406-417.
35. Grover S, Rahma OE, Hashemi N, Lim RM. Gastrointestinal and hepatic toxicities of checkpoint inhibitors: algorithms for management. *Am Soc Clin Oncol Educ Book*. 2018;38:13-19.
36. Tandon P, Bourassa-Blanchette S, Bishay K, Parlow S, Laurie SA, McCurdy JD. The risk of diarrhea and colitis in patients with advanced melanoma undergoing immune checkpoint inhibitor therapy: a systematic review and meta-analysis. *J Immunother*. 2018;41(3):101-108.
37. Wang DY, Ye F, Zhao S, Johnson DB. Incidence of immune checkpoint inhibitor-related colitis in solid tumor patients: a systematic review and meta-analysis. *Oncoimmunology*. 2017;6(10):e1344805.
38. Dougan M, Wang Y, Rubio-Tapia A, Lim JK. AGA clinical practice update on diagnosis and management of immune checkpoint inhibitor colitis and hepatitis: expert review. *Gastroenterology*. 2021;160(4):1384-1393.
39. Shah R, Witt D, Asif T, Mir FF. Ipilimumab as a cause of severe pan-colitis and colonic perforation. *Cureus*. 2017;9(4):e1182.
40. Dilling P, Walczak J, Pikiel P, Kruszewski WJ. Multiple colon perforation as a fatal complication during treatment of metastatic melanoma with ipilimumab—case report. *Pol Przegl Chir*. 2014;86(2):94-96.
41. Burdine L, Lai K, Laryea JA. Ipilimumab-induced colonic perforation. *J Surg Case Rep*. 2014;2014(3):rju010.
42. Savarese D. Common terminology criteria for adverse events. UpToDate. Published June 16, 2021. Accessed July 9, 2021. https://www.uptodate.com/contents/common-terminology-criteria-for-adverse-events.
43. Eshet Y, Baruch EN, Shapira-Frommer R, et al. Clinical significance of pan-

creatic atrophy induced by immune-checkpoint inhibitors: a case-control study. *Cancer Immunol Res*. 2018;6(12):1453-1458.
44. Badran YR, Shih A, Leet D, et al. Immune checkpoint inhibitor-associated celiac disease. *J Immunother Cancer*. 2020;8(1):e000958.
45. Marthey L, Mateus C, Mussini C, et al. Cancer immunotherapy with anti-CTLA-4 monoclonal antibodies induces an inflammatory bowel disease. *J Crohns Colitis*. 2016;10(4):395-401.
46. Collins M, Soularue E, Marthey L, Carbonnel F. Management of patients with immune checkpoint inhibitor-induced enterocolitis: a systematic review. *Clin Gastroenterol Hepatol.* 2020;18(6):1393-1403.e1.
47. Hughes MS, Molina GE, Chen ST, et al. Budesonide treatment for microscopic colitis from immune checkpoint inhibitors. *J Immunother Cancer*. 2019;7(1):292.
48. Mooradian MJ, Wang DY, Coromilas A, et al. Mucosal inflammation predicts response to systemic steroids in immune checkpoint inhibitor colitis. *J Immunother Cancer*. 2020;8(1):e000451.
49. Jain A, Lipson EJ, Sharfman WH, Brant SR, Lazarev MG. Colonic ulcerations may predict steroid-refractory course in patients with ipilimumab-mediated enterocolitis. *World J Gastroenterol.* 2017;23(11):2023-2028.
50. Wright AP, Piper MS, Bishu S, Stidham RW. Systematic review and case series: flexible sigmoidoscopy identifies most cases of checkpoint inhibitor-induced colitis. *Aliment Pharmacol Ther*. 2019;49(12):1474-1483.
51. Gonzalez RS, Salaria SN, Bohannon CD, Huber AR, Feely MM, Shi C. PD-1 inhibitor gastroenterocolitis: case series and appraisal of 'immunomodulatory gastroenterocolitis'. *Histopathology*. 2017;70(4):558-567.
52. Herlihy JD, Beasley S, Simmelink A, et al. Flexible sigmoidoscopy rather than colonoscopy is adequate for the diagnosis of ipilimumab-associated colitis. *South Med J*. 2019;112(3):154-158.
53. Nishida T, Iijima H, Adachi S. Immune checkpoint inhibitor-induced diarrhea/colitis: endoscopic and pathologic findings. *World J Gastrointest Pathophysiol*. 2019;10(2):17-28.
54. Abu-Sbeih H, Ali FS, Luo W, Qiao W, Raju GS, Wang Y. Importance of endoscopic and histological evaluation in the management of immune checkpoint inhibitor-induced colitis. *J Immunother Cancer*. 2018;6(1):95.
55. Cramer P, Bresalier RS. Gastrointestinal and hepatic complications of immune checkpoint inhibitors. *Curr Gastroenterol Rep*. 2017;19(1):3.
56. Zou F, Wang X, Glitza Oliva IC, et al. Fecal calprotectin concentration to assess endoscopic and histologic remission in patients with cancer with immune-mediated diarrhea and colitis. *J Immunother Cancer*. 2021;9(1):e002058.
57. Chen JH, Pezhouh MK, Lauwers GY, Masia R. Histopathologic features of colitis due to immunotherapy with anti-PD-1 antibodies. *Am J Surg Pathol*. 2017;41(5):643-654.
58. Verschuren EC, van den Eertwegh AJ, Wonders J, et al. Clinical, endoscopic, and histologic characteristics of ipilimumab-associated colitis. *Clin Gastroenterol Hepatol*. 2016;14(6):836-842.
59. Berman D, Parker SM, Siegel J, et al. Blockade of cytotoxic T-lymphocyte antigen-4 by ipilimumab results in dysregulation of gastrointestinal immunity in patients with advanced melanoma. *Cancer Immun.* 2010;10:11.
60. Puzanov I, Diab A, Abdallah K, et al; Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;5(1):95.
61. Brahmer JR, Lacchetti C, Schneider BJ, et al; National Comprehensive Cancer Network. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36(17):1714-1768.
62. Powell N, Ibraheim H, Raine T, et al. British Society of Gastroenterology endorsed guidance for the management of immune checkpoint inhibitor-induced enterocolitis. *Lancet Gastroenterol Hepatol*. 2020;5(7):679-697.
63. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Published November 27, 2017. Accessed March 1, 2021. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.
64. Thompson JA, Schneider BJ, Brahmer J, et al. NCCN guidelines insights: management of immunotherapy-related toxicities, version 1.2020. *J Natl Compr Canc Netw*. 2020;18(3):230-241.
65. Beck KE, Blansfield JA, Tran KQ, et al. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol*. 2006;24(15):2283-2289.
66. Johnson DH, Zobniw CM, Trinh VA, et al. Infliximab associated with faster symptom resolution compared with corticosteroids alone for the management of immune-related enterocolitis. *J Immunother Cancer*. 2018;6(1):103.
67. Abu-Sbeih H, Ali FS, Alsaadi D, et al. Outcomes of vedolizumab therapy in patients with immune checkpoint inhibitor-induced colitis: a multi-center study. *J Immunother Cancer*. 2018;6(1):142.
68. Zou F, Faleck DM, Thomas AS, et al. Efficacy and safety of vedolizumab and infliximab treatment for immune-mediated diarrhea and colitis in cancer patients: a multi-center study. Posted March 2, 2021. Accessed July 26, 2021. Available at SSRN: https://ssrn.com/abstract=3796123 or https://dx.doi.org/10.2139/ssrn.3796123.
69. Wang Y, Wiesnoski DH, Helmink BA, et al. Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. *Nat Med*. 2018;24(12):1804-1808.
70. Thomas AS, Ma W, Wang Y. Ustekinumab for refractory colitis associated with immune checkpoint inhibitors. *N Engl J Med*. 2021;384(6):581-583.
71. Bishu S, Melia J, Sharfman W, Lao CD, Fecher LA, Higgins PD. Efficacy and outcome of tofacitinib in immune checkpoint inhibitor colitis. *Gastroenterology.* 2021;160(3):932-934.e3.
72. Esfahani K, Hudson M, Batist G. Tofacitinib for refractory immune-related colitis from PD-1 therapy. *N Engl J Med*. 2020;382(24):2374-2375.
73. Abu-Sbeih H, Faleck D, Ricciuti B, et al. Immune checkpoint inhibitor therapy in patients with preexisting inflammatory bowel disease. *J Clin Oncol*. 2020;38(6):576-583.
74. Neto MBB, Ramos GP, Loftus EV Jr, Faubion WA, Raffals LE. Use of immune checkpoint inhibitors in patients with pre-established inflammatory bowel diseases: retrospective case series. *Clin Gastroenterol Hepatol*. 2021;19(6):1285-1287.e1.
75. Kähler KC, Eigentler TK, Gesierich A, et al; German Dermatologic Cooperative Oncology Group (DeCOG). Ipilimumab in metastatic melanoma patients with pre-existing autoimmune disorders. *Cancer Immunol Immunother*. 2018;67(5):825-834.
76. Johnson DB, Sullivan RJ, Ott PA, et al. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. *JAMA Oncol*. 2016;2(2):234-240.
77. Grover S, Ruan AB, Srivoleti P, et al. Safety of immune checkpoint inhibitors in patients with pre-existing inflammatory bowel disease and microscopic colitis. *JCO Oncol Pract*. 2020;16(9):e933-e942.
78. Weber J, Thompson JA, Hamid O, et al. A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. *Clin Cancer Res*. 2009;15(17):5591-5598.
79. Abu-Sbeih H, Ali FS, Naqash AR, et al. Resumption of immune checkpoint inhibitor therapy after immune-mediated colitis. *J Clin Oncol*. 2019;37(30):2738-2745.
80. Badran YR, Cohen JV, Brastianos PK, Parikh AR, Hong TS, Dougan M. Concurrent therapy with immune checkpoint inhibitors and TNFα blockade in patients with gastrointestinal immune-related adverse events. *J Immunother Cancer*. 2019;7(1):226.