MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER (MASCC) 2020 CLINICAL PRACTICE RECOMMENDATIONS FOR THE MANAGEMENT OF SEVERE GASTROINTESTINAL AND HEPATIC TOXICITIES FROM CHECKPOINT INHIBITORS

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All of the authors contributed equally to the conceptualization of the manuscript; MD drafted the manuscript, while BLR and DBJ provided clinical input and BLR, DBJ and RA editorial oversight. All of the authors provided critical appraisal of the manuscript and approve of its submission.

Acknowledgments

Professor BL Rapoport is supported by supported by the Cancer Association of South Africa (CANSA) and the National Research Foundation (NRF) of South Africa.

Dr. I. Glezerman is supported by the NIH/NCI (Cancer Center Support Grant P30 CA008748)

Running title: Immune-mediated severe gastrointestinal and hepatic toxicities

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Abstract

Immune-related adverse events (IrAEs) affecting the gastrointestinal (GI) tract and liver are among the most frequent and most severe inflammatory toxicities from contemporary immunotherapy. Inflammation of the colon and or small intestines (entero)colitis is the single most common GI IrAE and is an important cause of delay of discontinuation of immunotherapy. The severity of these GI IrAEs can range from manageable with symptomatic treatment alone to life-threatening complications, including perforation of liver failure. The frequency and severity of GI IrAEs is dependent on the specific immunotherapy given, with cytotoxic T lymphocyte antigen (CTLA)-4 blockade more likely to induce severe GI IrAEs than blockade of either programmed cell death protein 1 (PD-1) or PD-1 ligand (PD-L1), and combination therapy showing the highest rate of GI IrAEs, particularly in the liver. To date, we have minimal prospective data on the appropriate diagnosis and management of GI IrAEs, and recommendations are based largely on retrospective data and expert opinion. Although clinical diagnoses of GI IrAEs are common, biopsy is the gold standard for diagnosis of both immunotherapy-induced enterocolitis and hepatitis and can play an important role in excluding competing, though less common, diagnoses and ensuring optimal management. GI IrAEs typically respond to high dose corticosteroids, though a significant fraction of patients requires secondary immune suppression. For colitis, both TNF-α blockade with infliximab and integrin inhibition with vedolizumab have proved highly effective in corticosteroid-refractory cases. Detailed guidelines have been published for the management of low-grade GI IrAEs. In the setting of more severe toxicities, involvement of a GI specialist is generally recommended. The purpose of this review is to survey the available literature and provide management recommendations focused on the GI specialist.

Keywords: checkpoint blockade, colitis, enterocolitis, gastrointestinal immune-related adverse events, hepatitis, immune-related adverse events, immunotherapy

Introduction

Inflammation in the gastrointestinal (GI) tract and liver are among the most common immune-related adverse events (IrAEs) resulting from inhibitors of the immune checkpoints cytotoxic T lymphocyte antigen (CTLA)-4, programmed cell death protein 1 (PD-1), and PD-1 ligand (PD-L1) [1]. These toxicities can occur throughout the GI tract from stomach to rectum, and can, less commonly, involve the hepatic parenchyma, biliary tree, pancreas, and potentially the gallbladder [1-5]. The mechanisms underlying these inflammatory toxicities are poorly understood, but they are presumed to arise from inhibition of the regulatory mechanisms responsible for preventing T cell immunity to self-antigens and/or commensal microbes [6]. This is consistent with the predominantly lymphocytic inflammation seen on histopathology [7,8].

The purpose of these practice recommendations is to provide an overview of the gastrointestinal and hepatic complications of immune checkpoint blockade, including recommendations for diagnosis and for treatment. These practice recommendations will focus specifically on the management of advanced complications that typically require involvement of a gastroenterologist or hepatologist, may benefit from endoscopic evaluation, and may not respond to initial treatment strategies.

Checkpoint inhibitor colitis

Inflammation in the colon (colitis), with or without accompanying inflammation in the small intestine (enterocolitis), is the most common gastrointestinal IrAE associated with current immunotherapies [1,9-12]. Although isolated colitis is more common than enteritis, the precise frequencies are not yet established [1,9-12]. Patients can also develop enteritis without colitis, as well as gastroenteritis [1,13]. Isolated, symptomatic gastritis is less common [1,14-16]. In addition to enteritis, a small portion of patients present with newly symptomatic celiac disease, though whether this represents *de novo* disease or worsening of underlying, undiagnosed celiac disease is unknown [1].

The severity of GI IrAEs can range from readily manageable with lifestyle modification and symptom-directed treatment to life- threatening complications such as perforation [1,9-12,17]. Stricturing disease is rare, and fistulizing disease, a common variant of the inflammatory bowel disease, Crohn's disease, does not appear to occur [1, 9-12, 18]. The most common presenting symptom of checkpoint inhibitor (entero)colitis is watery, non-bloody diarrhea [1, 9-12, 19]. In clinical trials and most retrospective studies, diarrhea severity is rated using the Common Terminology Criteria for Adverse Events (CTCAE) using a grade 1 (mild) to grade 5 (death) scale [1, 20-22]. In its mildest form (grade 1), diarrhea from checkpoint inhibitor (entero)colitis presents as <4 extra bowel movements a day, rarely occurring overnight and often associated with eating [1,20-22]. As symptoms escalate to 4 to 6 extra bowel movements a day, they are defined as grade 2 symptoms [1, 20-22]. These patients often have cramping and urgency, but bleeding is rare [1, 9-12, 19-22]. Grade 3 diarrhea (> 7 extra bowel movements a day) typically presents with cramping, urgency, and can include nocturnal bowel movements and incontinence [1, 9-12, 19-22]. Fevers, severe abdominal pain, and hemodynamic instability are uncommon, but are more often components of grade 4 diarrhea. Deaths from enterocolitis have been reported, but are rare [1, 9-12, 19-22].

Because upper intestinal inflammation happens in a portion of patients with colitis, nausea, vomiting, and decreased appetite can also occur [1, 20-22]. Patients who have isolated gastritis or duodenitis can present primarily with upper GI symptoms, such as nausea and vomiting, epigastric pain, decreased appetite or weight loss [1, 13]. Although many patients with isolated upper GI inflammation have some diarrhea, some will have normal bowel movements [1, 13]. Bleeding is less frequent in immunotherapy-induced (entero)colitis than in other forms of colitis, and is often indirectly related to the severity of the colitis, representing hemorrhoids, dermal irritation, or metastatic disease [1, 20-22]. Constipation can occur in patients on immunotherapy, although the degree to which these cases are inflammatory in etiology is unclear, and constipation that rises to the level of medical intervention involving a subspecialist is rare [1].

Blockade of CTLA-4 leads to more frequent IrAEs, often severe IrAEs, in the GI tract than does blockade of PD-1 or PD-L1, though mild GI IrAEs are seen for both [1, 20-22]. Ipilimumab, the only currently approved antibody that targets CTLA-4, causes gastrointestinal symptoms in about 40% of patients when given at the 3 mg/kg standard dose for melanoma [1, 20-23]. The frequency of these symptoms is directly dependent on ipilimumab dose, with the adjuvant melanoma dose of 10 mg/kg having a substantially higher incidence of GI adverse events than occurs with the 3 mg/kg or 1 mg/kg doses [23,24]. Severe inflammation that requires urgent management is less common than milder GI inflammation, but still occurs in 10-15% of patients on ipilimumab [1,20-24].

Patients on PD-L1 inhibitors also have a fairly high incidence of mild GI symptoms with about 20% of patients developing diarrhea of any grade [1,20-23]. Severe GI toxicities are much less frequent, however, affecting 2-5% of patients [1,20-23]. At this point, no direct comparisons among the various PD-1 and PD-L1 inhibitors are available, but comparisons across trials suggest that GI IrAEs are reasonably uniform among the available drugs, and are not substantially affected by whether PD-1 or PD-L1 is the target [1,20-23].

Toxicity from combination checkpoint inhibitor therapy is at least additive, and there may be some synergistic effects on the frequency and severity of GI IrAEs [1]. Diarrhea occurs in about half of patients who receive ipilimumab and nivolumab in combination at the standard melanoma dosing (3 mg/kg ipilimumab and 1 mg/kg nivolumab), with severe GI toxicities occurring in 15-20% of patients [1,25]. At the lower doses of ipilimumab (1 mg/kg) used in the more recent regimens (RCC, MSI-hi CRC, lung cancer, *etc*), severe GI toxicities occur in closer to 5% of combination treated patients [26-29].

For patients with mild symptoms (grade 1 and some grade 2), diagnosis is often made clinically based on suggestive symptoms (*e.g.* new onset diarrhea) in the setting of immunotherapy treatment without another obvious etiology [1,20-22]. Infectious causes

are important to exclude, as this population is at increased risk for hospital/medical setting acquired infections [1,20-22]. Depending on the context and pre-test probability as assessed by the treating clinician, stool cultures, stool ova and parasite testing, and testing for *Clostridium difficile* should all be considered as part of the initial diagnostic evaluation [1,20-22]. In many cases, suggestive symptoms and the exclusion of infections are sufficient to diagnose a patient with a grade 1-2 GI toxicity, which will then typically be managed by the oncology treatment team [1,20-22].

Cross-sectional imaging can have a role in the diagnosis of colitis from checkpoint inhibitors [30-32]. Although the standard appearance is indistinguishable from other forms of colitis (*i.e.* infectious, ischemic), in a retrospective review of patients on ipilimumab with new onset diarrhea referred for imaging by computed tomography (CT) of the abdomen and a colonoscopy, the CT scan was found to be 85.2% sensitive and 75% specific for the presence of colitis [30-32]. This corresponded to a positive predictive value of 95.8% and a negative predictive value of 42.9% [30]. Whether these test characteristics are applicable to PD-1/PD-L1 colitis is unclear at present. Overall, these findings suggest that cross-sectional imaging is valuable for confirming the diagnosis of checkpoint inhibitor enterocolitis in patients with a high clinical likelihood of having the disease, but that CT has limited utility in excluding enterocolitis.

Endoscopic biopsies are the gold standard for diagnosis of GI IrAEs from checkpoint inhibitors, though the importance of endoscopy and tissue biopsies in the evaluation and treatment of these patients has not been rigorously examined [1, 20-22, 33]. The differential diagnosis in patients with suspected GI toxicities from immunotherapy includes checkpoint inhibitor (entero)colitis (the most likely diagnosis), as well as isolated checkpoint inhibitor (gastro)enteritis[1, 9-13, 33]. Complications of the malignancy itself can present similarly to inflammatory toxicities [34]. Infections are rare, but important causes of GI symptoms in patients on immunotherapy, as are side-effects from concurrent medications, and other sporadic GI illnesses such as diverticulitis and ischemic colitis [1,35,36]. Celiac disease can rarely present as new diarrhea in this population, as can pancreatic insufficiency [1, 2, 37, 38].

Most patients with checkpoint inhibitor (entero)colitis, enteritis, or gastritis will respond to first line treatment with high dose corticosteroids and will achieve remission of inflammation after a 4-6 week corticosteroid taper [1,9-12]. Approximately 30-40% of patients with GI IrAEs from checkpoint inhibitors will require secondary immune suppression with a biologic agent [9]. The best studied biologic therapies are infliximab and vedolizumab, both commonly used for the treatment of inflammatory bowel disease (IBD) [1, 9-12, 39-44].

Recent retrospective analyses have demonstrated that endoscopic findings are the most important clinical factors for predicting resistance to first-line treatment with corticosteroids [10,12]. Specifically, the presence of colonic ulcerations on endoscopy suggests a more difficult treatment course [10,12]. Importantly, diarrhea grading as determined by the CTCAE was not predictive. Whether having this information prospectively can improve patient outcomes is unclear. However, a recent retrospective analysis found that patients who did receive endoscopic evaluation early in their treatment course tended to have faster symptom resolution and shorter duration exposure to immune suppression [33].

Checkpoint Inhibitor Hepatitis

Hepatitis is much less common than (entero)colitis in patients treated with either ipilimumab or PD-L1 monotherapy, but when combined with other agents, hepatitis is considerably more frequent [1,3]. Because of the lower incidence compared to (entero)colitis, at this time, much less is known about checkpoint inhibitor hepatitis diagnosis and management than is known for (entero)colitis. The incidence of hepatitis that is detectable on laboratory testing is <5% in clinical trials of checkpoint inhibitor monotherapy, and severe hepatitis is rare [1,3,45,46]. When ipilimumab is combined with nivolumab, the incidence of hepatitis rises to nearly 25% with severe hepatitis in 2-5% of cases [1, 3, 45, 46]. This level of synergy in a toxicity is uncommon with current immunotherapies, where many of the toxicities are usually additive in combination treatments [1, 3, 45, 46]. For this reason, the synergistic toxicity seen in patients for

hepatitis suggests that, in the liver, the PD-L1 and CTLA-4 pathways have important functional redundancy in maintaining immune homeostasis. When immunotherapies are combined with conventional chemotherapies or with targeted agents, liver injury also becomes significantly more common, suggesting that checkpoint inhibitors increase the sensitivity of the liver to other toxic insults [47-50].

Liver inflammation induced by immunotherapy is typically detected on routine monitoring and is rarely symptomatic [3,45,46]. However, patients with cancer are at increased risk for a wide variety of injuries to the liver, including metastatic spread, thromboembolic disease, biliary disease including obstruction, and infection, all of which can be symptomatic [3,45,46]. For this reason, careful evaluation of abnormal liver tests is essential to making a correct diagnosis and providing appropriate management [3]. In severe liver inflammation (grade 3-4), biopsies have an important role in confirming the diagnosis [3,20-22]. Typical histologic patterns of checkpoint inhibitor hepatitis have been described, though whether these patterns predict response to treatment or other outcomes is presently unknown [51-55]. Interestingly, although spontaneous autoimmune hepatitis (AIM) is a well-described syndrome that we might expect to resemble checkpoint inhibitor hepatitis histologically, the two diseases appear quite distinct [51-55]. AIM is characterized by an influx of plasma cells; checkpoint inhibitor hepatitis, on the other hand, is most typically a lymphocytic hepatitis, but can also appear as granulomatous inflammation, while fibrin ring granulomas are a described subtype of PD-1 hepatitis specifically [51-55]. Most patients with checkpoint inhibitor hepatitis will respond to corticosteroids, though a small fraction requires secondary immune suppression [3,20-22]. Several agents have been reported to be effective in these circumstances, including mycophenolate mofetil, tacrolimus, and azathioprine [3,20-22]. At present, we have no data to recommend one treatment over another, and all 3 are likely to have some deleterious effects on T cell immunity. Anti-thymocyte globulin (ATG) has been reported to be effective in a case of severe, fulminant hepatitis related to checkpoint inhibitors [56]. The role of infliximab in treating checkpoint inhibitor

hepatitis is presently unknown, though it is generally considered to be risky given the rare association between infliximab and acute liver injury [57].

Evaluation and Management of Luminal Toxicities from Immunotherapy

Current evaluation and management guidelines for GI adverse events from checkpoint inhibitors are based almost entirely on retrospective analysis and expert opinion [20-22]. One prospective study has been published evaluating enteric budesonide compared to placebo for the prevention of diarrhea and colitis associated with ipilimumab treatment [58]. This trial was negative and has generally led to the conclusion that budesonide is ineffective as treatment for immunotherapy-associated enterocolitis, although it has not been directly tested in the therapeutic (*i.e.* not prophylactic) setting [58].

Several comprehensive guidelines have been published recently that focus on evaluation and management of IrAEs directed toward the primary oncology team [20-22]. The CTCAE provides definitions for adverse events both based on symptoms (*e.g.* diarrhea) and clinicopathologic diagnoses (*e.g.* colitis). Generally, gastroenterologists will become involved when patients develop severe symptoms (CTCAE grade 2-4), and at the point where a pathologic diagnosis is required. Here we provide recommendations targeted toward the consulting gastroenterologist to assist in management of these more severe IrAEs in the GI tract. These recommendations focus on patients with (entero)colitis. Although enteritis and gastroenteritis can also occur in patients on immunotherapy, these other luminal inflammatory syndromes are less common, and are currently managed identically to enterocolitis due to paucity of clinical evidence comparing management strategies in each setting [1, 13, 20-22, 59].

Laboratory testing

Exclusion of infectious causes of diarrhea is important in all patients presenting with Grade 2-4 diarrhea on immunotherapy. This includes stool culture. Ova and parasite testing should be considered based on risk factors and local prevalence. *C Difficile* toxin

testing is also reasonable in this population, as all of these patients have hospital exposure, and many have had prior exposure to antibiotics.

Fecal calprotectin and lactoferrin are highly sensitive tests for colonic inflammation that are often used in inflammatory bowel disease to rule out luminal inflammation when triaging patients for colonoscopic evaluation [60]. Whether fecal calprotectin or lactoferrin can help stratify patients for endoscopic evaluation remains unclear at the moment, but it is a reasonable strategy if rapid testing is available. Calprotectin may also be useful in monitoring colitis response to treatment in addition to following symptom resolution [33]. Fecal elastase may also be appropriate as an early test in patients presenting with diarrhea on immunotherapy to exclude pancreatic insufficiency, particularly in patients who have not responded adequately to initial management with corticosteroids or who are presenting with steatorrhea [2]. Serological testing for celiac disease (tissue transglutaminase (TTG)-Immunoglobulin (Ig)A and total IgA) is reasonable, but we advocate confirmatory biopsies by EGD in patients with positive test results [1, 37, 38]. Importantly, both newly symptomatic celiac disease and pancreatic insufficiency occurring in the setting of checkpoint inhibitors may be steroid unresponsive [1, 2, 37, 38].

Because of the high risk that patients with immunotherapy-associated enterocolitis will require secondary immune suppression (between 30-40%), we advocate testing for hepatitis B (surface antigen, surface antibody, and core antibody) and for latent tuberculosis (either PPD, or tuberculosis ELISpot) at the time of initial evaluation for enterocolitis [9].

Endoscopy

Inflammation in the GI mucosa induced by immunotherapy targeting CTLA-4 and/or PD-L1 can involve any part of the GI tract from the stomach to the rectum [1,10,12]. Colitis or enterocolitis are the most common types of inflammation [1,10,12].

Although clinically important, symptoms and CTCAE grade correlate poorly with the extent and severity of mucosal injury found on endoscopy in patients with suspected checkpoint inhibitor colitis [61, 62]. Perhaps more importantly, symptoms also do not predict response to treatment [61, 62]. In contrast, the degree of mucosal injury found on endoscopy is the most predictive factor of treatment responsiveness [61, 62]. Endoscopic evaluation can be useful in identifying patients with milder symptoms who have significant mucosal injury [61]. These patients are less likely to respond to corticosteroids and may require secondary immune suppression [61]. They may also be at higher risk of developing complications should immunotherapy resume, though data addressing this question are currently lacking. At the same time, endoscopy can identify patients with severe symptoms and no visible mucosal injury (checkpoint microscopic colitis); patients with microscopic colitis may respond well to colonic formulations of budesonide alone [62].

In the great majority of patients, colonic inflammation involves the left colon, and while regional variability does occur, most patients can be diagnosed by directed biopsies of the left colon [1,7,10,12]. Thus, flexible sigmoidoscopy, which is both easier on the patient and less expensive than colonoscopy, is often sufficient for making a diagnosis. A portion of patients with luminal inflammation from immunotherapy will have findings isolated to the upper GI tract, although the precise frequency has not been defined [1,13, 59]. Esophagogastroduodenoscopy (EGD) is reasonable in patients who have had negative flexible sigmoidoscopies, but who have a sufficiently high likelihood of having luminal inflammation based on symptoms and history, potentially in conjunction with a full colonoscopy.

No guidelines have yet been developed describing appropriate biopsy numbers/coverage. We typically take four gastric biopsies, and four in the duodenum beyond the duodenal bulb during upper endoscopies. Esophagitis from immunotherapy is rare, and we do not biopsy the esophagus in the absence of mucosal changes or symptoms suggestive of esophagitis. In the colon, we typically collect 2-4 biopsies from the descending colon, sigmoid colon, and rectum and pool these unless regional

variation is observed on endoscopic evaluation. In the event of localized inflammation, we guide biopsies toward endoscopically abnormal tissue.

Initial Treatment with Corticosteroids

Currently we have no rigorous evidence supporting any specific management strategy for the GI toxicities of immunotherapy [9, 20-22, 39, 43, 44]. However, current guidelines universally recommend high-dose corticosteroids as initial management based on extensive experience from patients on immunotherapy clinical trials, as well as subsequent retrospective analyses [20-22] and are summarized in Table 1. Corticosteroids are often initiated by the primary oncology team using doses between 0.5 and 2 mg/kg of methylprednisolone or equivalent daily [20-22]. These are delivered intravenously to patients who are hospitalized. For outpatients, doses closer to those used for IBD (40-60 mg of prednisone) are generally effective [1,20-22]. Local treatment with colonic budesonide preparations were shown to be ineffective in prophylaxis of CTLA-4 blockade colitis, but may still have some role in treatment. Steroid tapers are typically performed over 4-6 weeks, depending on the severity of the initial inflammation and the rapidity of the initial response [1,20-22].

Approximately two thirds of patients will respond to initial management with corticosteroids and will not require any further treatment [1, 9, 20-22]. The remaining patients require escalation of immune suppression, which is generally done in consultation with a gastroenterologist [1,9,20-22].

Table 1: Management recommendations for gastrointestinal adverse events

Diarrhea or colitis grade (CTCAE version 5.0)	Laboratory testing*	Imaging	Endoscopy	Initial treatment	Management of first line treatment failure
1	TTG-IgA, IgA HepB sAg, sAb, cAb Testing for latent tuberculosis infection Consider: stool cultures. *C. difficile* testing and ova and parasite testing; fecal elastase; calprotectin or lactoferrin	Routine cross-sectional imaging is not recommended except where extraluminal complications such a perforation or abscess are of clinical concern	Consider only for patients with atypical presentations, including very early onset symptoms, or after discontinuation of immunotherapy	Empiric treatment with motility slowing agents such as loperamide or atropine-diphenoxylate	Manage as grade 2
2	TTG-IgA, IgA HepB sAg, sAb, cAb Testing for latent tuberculosis infection stool cultures. *C. difficile* testing Consider: ova and parasite testing; fecal elastase; calprotectin or lactoferrin	As grade 1	Consider flexible sigmoidoscopy prior to initiation of systemic corticosteroids; upper endoscopy or colonoscopy may be appropriate in patients with normal flexible sigmoidoscopies	Empiric treatment with motility slowing agents such as loperamide or atropine-diphenoxylate may be appropriate for patients where diarrhea is the only system Empiric systemic corticosteroids may be considered (0.5–1 mg/kg prednisone or equivalent daily followed by a 4–6 week taper) For patients with biopsy confirmed disease, systemic corticosteroid treatment is advised; patients with colonic ulceration should be considered for high-dose systemic corticosteroids (1–2 mg/kg prednisone or equivalent daily) and early induction of biologic therapy (either infliximab or vedolizumab)	Endoscopic biopsy confirmation of the diagnosis prior to escalation of therapy Consider fecal elastase and detection of CMV in the endoscopic biopsy either by cell culture or IHC. Add biological therapy (infliximab or vedolizumab)
3	As for grade 2	As for grade 1	Flexible sigmoidoscopy or colonoscopy should be strongly considered prior to initiation of systemic corticosteroids; upper endoscopy may be appropriate in patients with normal lower endoscopies	For patients with biopsy confirmed disease, systemic corticosteroid treatment is advised either oral or intravenous; patients with colonic ulceration should be considered for high-dose systemic corticosteroids (1–2 mg/kg prednisone or equivalent daily) starting with intravenous therapy, as well as early induction of biologic therapy (either infliximab or vedolizumab)	Consider fecal elastase and detection of CMV in the endoscopic biopsy either by cell culture or IHC. Add biological therapy (infliximab or vedolizumab)
4	As for grade 2	As for grade 1	As for grade 3	Consider hospitalization, otherwise as for grade 3	As for grade 3

TTG-IgA tissue transglutaminase-immunoglobulin A, *IgA* immunoglobulin A, *HepB* hepatitis B virus, *sAg* surface antigen, *sAb* surface antibody, *cAb* core antibody, *IHC* immunohistochemistry

*Routine monitoring of comprehensive metabolic panels, complete blood counts, and TSH are recommended for all patients undergoing immunotherapy

Escalation to Secondary Immune Suppression

For patients who do not respond adequately to corticosteroids, both infliximab and vedolizumab appear to have substantial efficacy in the treatment of enterocolitis associated with CTLA-4 or PD-L1 inhibitors individually or in combination [9, 20,21,22, 39, 43, 44, 63]. Alternative antibodies targeting tumor necrosis factor (TNF)α are likely to be effective, though clinical experience is minimal. Both agents are used at standard IBD doses, although infliximab can be dose-escalated in partial responders [9, 20,21,22, 39, 43, 44, 63].

The effectiveness of infliximab and vedolizumab has not been directly compared, but both appear to act rapidly, often within a week [9, 20,21,22, 39, 43, 44, 63]. Onset of symptom control is generally more rapid than would be expected when treating IBD [9, 20,21,22, 39, 43, 44, 63]. Optimal dose and schedule of secondary immune suppression is not established for either agent, though standard IBD dosing is typically sufficient [9, 20,21,22, 39, 43, 44, 63]. Between 1 and 3 infusions are typically sufficient for enterocolitis control for both vedolizumab and infliximab, and very few patients ever require maintenance therapy [9, 20,21,22, 39, 43, 44, 63]. Recommendations in respect of dose and duration are based on symptom control, with treatment continued only in those patients who have residual symptoms. The utility of calprotectin monitoring or follow-up endoscopy as strategies to guide this decision remains unclear, neither do we know how guided treatment schedules with variable doses compare with fixed doses with 3 infusions in patients irrespective of response.

Early initiation of secondary immune suppression is associated with faster symptom resolution, decreased hospitalization, and decreased risk of enterocolitis recurrence in retrospective analyses [44]. In general, the decision to start secondary immune suppression is made for two reasons: 1) inadequate response to initial treatment with corticosteroids, and 2) recurrence of enterocolitis symptoms during corticosteroid taper. We recommend using the grade of mucosal severity to guide the decision on how quickly to use secondary immune suppression. Patients who have ulcerating disease are treated within 72 hours of corticosteroid initiation if they do not have resolution back to grade 1 symptoms. For less of less severe enterocolitis longer duration of steroid treatment may be appropriate before determining that a patient is unresponsive [10,12]. Secondary immune suppression is initiated after reemergence of symptoms during a steroid taper. Following initiation of secondary immune suppression, the steroid dose is increased being equivalent to the last effective dose, with tapering commenced on resolution of symptoms.

Several factors should be considered in choosing between infliximab and vedolizumab as treatment for immune-related enterocolitis. Based on currently available evidence,

both drugs can be considered as equivalent first-line treatments [9, 20,21,22, 39, 43, 44, 63]. Infliximab is a systemically active immune suppressive agent that modulates immune responses, while vedolizumab blocks α4β7 integrin, which primarily affects the trafficking of lymphocytes into the gut. Consequently, patients with active infections of anatomical sites outside the GI tract may be more appropriately treated by vedolizumab. Additionally, vedolizumab should be avoided in patients with GI malignancies or metastases (approximately 5% of patients with melanoma) [34, 64]. The impact of these two drugs on antitumor immunity in humans is unknown, though vedolizumab is unlikely to have deleterious effects on antitumor immune responses outside of the gut. Blockade of TNFα with agents such as infliximab has been linked to improved antitumor responses in murine models of antitumor immunity [65, 66]. Infliximab has been associated with an increased incidence of melanoma in a meta-analysis of patients with IBD, but not in larger analyses of patients treated for rheumatologic conditions [67, 68]. Retrospective analyses of patients with melanoma treated with immunotherapy that developed colitis and received infliximab have shown no negative impact on tumor outcomes [42]. Irrespective of the aforementioned issues, drug availability and coverage are important considerations and may ultimately be the principal deciding factors for determining selection between infliximab and vedolizumab in most clinical scenarios.

Treatment of Patients Refractory to Initial Biologic Therapy

A small fraction of patients with immune-related enterocolitis will fail to respond to corticosteroids as well as infliximab or vedolizumab. In these patients, confirmation of ongoing inflammation and exclusion of opportunistic infections is essential. Based on patient risk factors, recommended investigations should include repeat stool cultures, *C Difficile* testing, as well as ova and parasite testing.

Although measurement of calprotectin or lactoferrin may be useful in suggesting ongoing luminal inflammation, endoscopy should be considered in all of these patients. These investigations are necessary to provide evidence of mucosal healing and to confirm ongoing inflammation histopathologically. Additional differential diagnoses

include cytomegalovirus (CMV) infection, other opportunistic viral infections, and fungal colitis. Provided that these infections are excluded, and ongoing significant inflammation is confirmed, escalation of immune suppression is appropriate.

Patients with immunotherapy-induced enterocolitis often do not have the time to wait for a full washout period before initiation of alternative immune suppression. Initiation of alternative immune suppression often begins within 2-4 weeks of treatment with the prior biologic therapy [39].

Current evidence, albeit limited, suggest that switching from infliximab to vedolizumab, or vice versa, is the most appropriate management strategy after failure of the initial choice of biologic therapy [39]. The response rates to third-line immune suppression are generally lower than would be expected for the same agent as second-line treatment. In patients who have failed both biologic therapies, fecal microbiota transplant (FMT) can be considered depending on accessibility [69]. Clinical trials are ongoing to determine whether FMT is appropriate as earlier management and to define response rates. FMT has shown some efficacy in IBD, but is known to be highly effective in *C. difficile* colitis, suggesting that colonic dysbiosis or occult infections may play an important role in driving ongoing inflammation in some patients with immune-related enterocolitis from immunotherapy [70, 71].

Whether other forms of immune suppression that are effective in IBD are also effective in immune-related enterocolitis is not clear. Mesalamine has been used in some cases of mild enterocolitis. Immunomodulatory drugs such as 6-mercaptopurine or methotrexate typically has a slow onset of therapeutic efficacy in IBD and may not act fast enough to be clinically useful in severe cases of immune-related enterocolitis. Although unproven, these drugs may also have a deleterious effect on the anti-tumor response.

In very refractory cases, alternative biologic agents such as ustekinumab would be reasonable to try, though currently we have no published evidence of efficacy [72]. Based on comprehensive analyses of the correlates of effective antitumor immunity and

the pathways of immunotherapy resistance, signaling through Janus kinase (JAK) kinases is likely to play an important role in anticancer treatment. Although JAK inhibitors (e.g. tofacitinib) present a potential therapeutic option, this remains to be proven and should be used with extreme caution in this patient population. Similarly, CTLA-4Ig (e.g. abatacept, belatacept) is likely to be effective in CTLA-4 blockade colitis, and potentially PD-1 blockade colitis, given its efficacy in colitis associated with CTLA-4 haploinsufficiency [73,74,75,76,77,78,79,80]. Yet the mechanism of action of CTLA-4Ig also means that it is likely to interfere with effective antitumor responses. All the abovementioned strategies are not proven and requires clinical studies to confirm the efficacy.

Grading Based Treatment Algorithm

Although the following algorithm focuses on diarrhea as the presenting symptom, other GI symptoms such as nausea, vomiting, and decreased appetite can be managed similarly. For primarily upper GI symptoms, upper endoscopy is favored over lower endoscopy for evaluation. For patients with decreased appetite, weight loss, or abdominal pain, cross-sectional imaging has a critical role in management for any severe (grade 3-4) symptoms. The rationale for these grading-based recommendations is presented in detail in the preceding sections (Table 1).

Grade 1 Diarrhea

Low-grade diarrhea - somewhere between 1 and 3 extra bowel movements a day – is frequent with current immunotherapy and is managed with symptomatic control. This can include motility slowing agents such as loperamide or diphenoxalate-atropine, dietary modification including bulking agents like psyllium, and lifestyle changes. Immunotherapy is generally continued for grade 1 symptoms. In addition to diarrhea, low-grade nausea, vomiting, and decreased appetite can all occur from immunotherapy, as can, albeit less frequently, pain and cramping.

Grade 2 Diarrhea

The evaluation and management of grade 2 diarrhea (4 to 7 addition bowel movements a day) is less well established. This is similar for nausea, vomiting, and decreased appetite. Many of these patients are managed by their oncology teams through temporary holding of immunotherapy and empiric treatment courses with corticosteroids. However, some of these patients are referred to subspecialists for tissue diagnoses. In these instances, the endoscopy can be valuable for two reasons. The first is to identify those patients who do not have mucosal inflammation at all. In these patients, corticosteroids are not likely to be beneficial, and alternative treatments can be considered. Because symptoms correlate poorly with the extent and severity of mucosal disease and do not predict response to therapy, endoscopic evaluation plays an important role in management decisions. The identification of mucosal ulcerations increases the likelihood that a patient will require secondary immune suppression to control checkpoint colitis, while identification of microscopic colitis may indicate responsiveness to colonic formulations for budesonide.

Corticosteroids are first-line therapy for biopsy proven grade 2 enterocolitis. No rigorous studies have examined steroid dose. Typically, patients will respond to doses in the range of 0.5-1 mg/kg oral prednisone or, for inpatients, intravenous methylprednisolone. Doses of 40-60 mg of oral prednisone many also be effective in many cases. Steroid tapers generally occur over a 4-6 week period and can be guided by the severity of mucosal inflammation observed on biopsy, with slower tapers for patients with colonic ulcers, and rapid tapers for patients who have histologic inflammation without endoscopic evidence of inflammation.

Grade 3/4 Diarrhea

Grade 3 diarrhea is often managed in conjunction with a specialist in gastroenterology. Patients can have grade 3 diarrhea either because they failed to respond to initial management for grade 2 diarrhea, or because they initially present with severe diarrhea (> 7 extra bowel movements a day). Grade 4 diarrhea is associated with life-threatening

complications such as end-organ injury, severe hypotension, anemia, *etc.* Many of these patients have significant mucosal inflammation, and endoscopic evaluation is recommended in all of them, ideally prior to initiation of corticosteroids.

The purpose of endoscopy in this group of patients is several-fold. First, a small, but significant subset of these patients will have an alternative cause for their diarrhea. This includes infectious and ischemic colitis, new onset celiac disease, pancreatic insufficiency (endoscopically normal), and other medication-induced diarrhea (which will often show minimal mucosal changes) [2, 61, 62, 81]. This is particularly important in patients who are initially referred to a gastroenterologist after having failed first-line corticosteroids. The second reason for endoscopic evaluation is to determine mucosal severity. Similar to the rationale for grade 2 symptoms, determining which of these patients has severe mucosal injury can help guide the transition to more rapid initiation of secondary immune suppression [61] and identifying microscopic colitis can help avoid systemic corticosteroids altogether [62].

Corticosteroids remain first-line therapy for biopsy proven grade 3/4 enterocolitis, although initial corticosteroid doses are typically 1–2 mg/kg methylprednisolone or equivalent. Some evidence suggests that earlier initiation of secondary immune suppression may be beneficial in patients with more severe GI adverse events, though this evidence is largely based on mucosal severity rather than the severity of the presenting symptoms.

Hepatitis

Hepatitis Grade 1: ALT/AST upper limit of normal (ULN) to 3 x ULN, ALKP ULN to 2.5 x ULN, TBILI ULN to 1.5 x ULN

Recommendations (Table 2): Frequent blood monitoring is indicated (1-2 x weekly). A patient history of concomitant drugs usage (including all over-the-counter medications), herbal supplements, as well as alcohol use should be obtained. Immunotherapy does not need to be delayed, and sub-specialists are typically not involved.

Table 2. Management recommendations for hepatic adverse events

Diarrhea or colitis grade (CTCAE version 5.0)	Laboratory testing*	Imaging	Endoscopy	Initial treatment	Management of first line treatment failure
1	Increase frequency of liver testing (ALT, AST, ALKP, TBILI, DILI) to weekly or twice weekly	None recommended	Obtain history of alcohol exposure, new medications, and herbal supplement use	Stop potentially hepatotoxic concomitant medications and supplements, advise against alcohol use	N/A
2	Twice weekly liver testing Hepatitis A IgM and IgG, hepatitis B core antibody, surface antibody, surface antigen; hepatitis C antibody; EBV and CMV serologies (IgM/IgG) ANA, ASMA, AMA, iron, TIBC, ferritin Consider ceruloplasmin and A1AT	Right upper quadrant ultrasound with vascular flow measurement Consider MRCP and or EUS if predominantly ALKP/TBILI elevation Consider cross sectional imaging for patients with abdominal malignancies or with hepatic metastases hepatic metastases	History as for grade 1 Consider liver biopsy	0.5–1 mg/kg daily prednisone or prednisone equivalent Hold immunotherapy until resolution to grade 1 or less	Liver biopsy if not already obtained Start secondary immune suppression with one of the following: Azathioprine 1–2 mg/kg daily, mycophenolate mofetil 500–1000 mg BID, tacrolimus (goal level 8–10 ng/mL or lower if early response
3	As for grade 2 with daily or every other day liver tests	As for grade 2	History as for grade 1 Liver biopsy to confirm diagnosis	0.5–2 mg/kg BID prednisone or prednisone equivalent Discontinue immunotherapy	Start secondary immune suppression with one of the following: Azathioprine 1–2 mg/kg daily, mycophenolate mofetil 500–1000 mg BID, tacrolimus (goal level 8–10 ng/mL or lower if early response Triple therapy may be considered in refractory cases
4	As for grade 2 with daily liver tests Check acetaminophen level	As for grade 2	As for grade 3	0.5–2 mg/kg BID prednisone or prednisone equivalent Consider hospitalization for IV steroids and close monitoring Discontinue immunotherapy	Start secondary immune suppression with one of the following: Azathioprine 1–2 mg/kg daily, mycophenolate mofetil 500–1000 mg BID, tacrolimus (goal level 8–10 ng/mL or lower if early response Triple therapy may be considered in refractory cases Antithymocyte globulin may be considered in rapidly progressing hepatitis

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *ALKP* alkaline phosphatase, *TBILI* total bilirubin, *DBILI* direct bilirubin, *IgM* immunoglobulin M, *IgG* immunoglobulin G, *EBV* Epstein-Barr virus, *CMV* cytomegalovirus, *ANA* antinuclear antibody, *ASMA* anti-smooth muscle antibody, *AMA* anti-mitochondrial antibody, *TIBC* total iron binding capacity, *A1AT* alpha-1 anti-trypsin, *MRCP* magnetic resonance cholangiopancreatography, *EUS* endoscopic ultrasound

Hepatitis Grade 2: ALT/AST >3 – 5 x ULN, ALKP >2.5 – 5 x ULN, TBILI >1.5 – 3 x ULN

Recommendations: Twice weekly monitoring, and withholding immunotherapy. Patients with grade 2 hepatitis should be investigated for potential non-immune mediated etiologies. These investigation includes a right upper quadrant ultrasound, hepatitis A, B, and C serology, Epstein-Barr virus (EBV) and CMV testing. Autoimmune disease serology, iron studies, and measurement of ceruloplasmin, and alpha-1-antitrypsin (A1AT) testing (in selected patients based on prior history). As for all patients with abnormal liver testing results, concomitant medications and alcohol use should be

assessed. For patients with a predominantly cholestatic hepatitis, advanced imaging of the biliary tract should be considered such as magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) if indicated. Patients with abdominal malignancies or known hepatic metastases should also undergo cross-sectional imaging. For patients without another clear etiology for their hepatitis and with a predominantly hepatocellular pattern of injury, checkpoint hepatitis is the most likely diagnosis and empiric treatment with 0.5 – 1 mg/kg prednisone or prednisone equivalent is a reasonable treatment option. Whether biopsy should be obtained prior to initiation of corticosteroids in these patients is presently unclear. For patients who do not respond within one week to corticosteroids with a least a 50% reduction in laboratory values, a biopsy is indicated to confirm the diagnosis. Secondary immune suppression should be considered if the diagnosis is confirmed. Azathioprine [1-2 mg/kg), mycophenolate mofetil (500 – 1000 mg BID), and tacrolimus [targeting blood levels of 8-10 nanograms (ng)/ml or lower if a response is detected early] have all been used as secondary immune suppression in these patients even though optimal doses and dosing schedules have not been determined.

Grade 3/4: ALT/AST >5 x ULN, ALKP >5 x ULN, TBILI >3 x ULN

Recommendations: Patients with higher-grade hepatic injury will typically be referred to Hepatology. In addition to all of the considerations for grade 2 hepatic injury, we recommend performing biopsies on all of these patients to exclude a non-immune-mediated cause of the liver injury, given the severity of the detected laboratory changes, and the potential clinical impact of missing an alternative diagnosis. Treatment for confirmed Grade 3/4 checkpoint hepatitis is similar to that of Grade 2 hepatitis, though doses of corticosteroid as high as 2 mg/kg could be considered in severe cases. Failure to respond within one week to corticosteroids with at least a 50% reduction in laboratory values should prompt the addition of secondary immune suppression. Azathioprine (1-2 mg/kg), mycophenolate mofetil (500 – 1000 mg BID), and tacrolimus (targeting blood levels or 8-10 ng/ml or lower if a response is detected early) have all been used as

secondary immune suppression in these patients even though, as mentioned above, optimal doses and dosing schedules remains to be determined. In severe, fulminant hepatitis, ATG is another treatment option. The role of infliximab in the management of immune-checkpoint hepatitis remains unclear.

Conclusions

Immune-mediated adverse events in the GI tract and liver are important limitations on current checkpoint inhibitor therapies. Although we are beginning to develop a robust understanding of the clinical presentations of these IrAEs, our understanding of the immune mechanisms that drive them remains inconclusive. Several empiric treatments have been developed for these toxicities. These appear to have reasonable efficacy based on retrospective analyses, although optimal diagnostic and treatment strategies have not been established in prospective clinical trials. For this reason, we do not yet know if any specific treatment strategy is more efficacious than another. Moreover,there is a a limited understanding of how these GI and hepatic irAEs affect cancer treatment outcomes, and how treatment of these IrAEs may influence the anti-tumor immune response.

Future work should focus on developing a clear understanding of the immune mechanisms that drive GI and hepatic IrAEs. Clinical trials should prospectively compare various treatment strategies using both organ-specific outcomes (*e.g.* resolution of colitis), and tumor-specific outcomes (*e.g.* progression-free and overall survival). These trials will be necessary for the establishment of truly evidence-based recommendations to optimize outcomes for these patients.

Conflict of interest

AB, RA, JC, TC, PG, DG and VRS have no conflict of interest to declare. MD reports grants from Novartis, other (SAB) from Neoleukin Therapeutics, personal fees from Partner Therapeutics, personal fees from Tillotts Pharma, grants from Genentech, outside the submitted work. MG reports consultant work with Bristol Myers Squibb

(BMS), and AstraZeneca, outside the submitted work. IG reports other (Stock Ownership) from Pfizer Inc., personal fees from CytomX Inc, outside the submitted work. DBJ reports other (advisory board) from Array Biopharma, grants and other (advisory board) from BMS, other (advisory board) from Jansen, grants from Incyte, other (advisory board) from Merck, other (advisory board) from Novartis, outside the submitted work. In addition, DBJ has a patent Co-inventor on use of CTLA-4 agonist for IAEs pending. BLR reports personal fees and other (advisory board) from Merck and Co, grants, personal fees and other (advisory board) from BMS, grants, personal fees and other (advisory board) from Roche South Africa, personal fees and other (advisory board) from AstraZeneca, during the conduct of the study. MSA reports personal fees from Gilead, grants from Pfizer, personal fees from Abbvie, outside the submitted work.

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