Immune-Mediated Colitis

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Abstract

Purpose of review This review addresses our current knowledge of immune-mediated colitis (IMC) and offers a practical guide to its management.
Recent findings Due to the similarity in clinical, endoscopic, and histologic findings between IMC and inflammatory bowel disease (IBD), gastroenterologists have tailored their approach to IMC management to that of IBD.
Summary Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that augment the T-cell anti-tumor response of the immune system and have demonstrated their importance in the treatment of a wide range of malignancies. With the growing benefits of ICIs, there are immune-related adverse events (irAEs) that mirror many known autoimmune diseases. Diarrhea and IMC are the most common and severe irAEs noted. No standardized guidelines exist in the management of these irAEs.

Introduction

Over the past several years, immune checkpoint inhibitors (ICIs) have had growing success in the treatment of a wide range of malignancies and have changed the treatment landscape in oncology. Cancer cells often use checkpoint molecules, such as cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed cell death ligand-1 (PD-L1), to evade attack from the immune system and allow for uninterrupted multiplication. ICIs inhibit these checkpoint pathways by blocking ligands or proteins that would otherwise lead to inactivation or death of anti-tumor T cells, which in turn allow T cells to destroy the cancer cells [1•, 2].

The United States Food and Drug Administration (FDA) has approved several ICIs in the treatment of solid tumors and hematologic malignancies. Ipilimumab, an anti-CTLA-4 monoclonal antibody, was the first ICI approved for use in patients with malignant melanoma [3, 4••]. Pembrolizumab and nivolumab, agents that target

PD-1, were subsequently approved in the treatment of melanoma. ICIs have now become the treatment of choice in several cancers including nonsmall cell lung cancer (NSCLC), Hodgkin lymphoma, renal cell carcinoma, hepatocellular carcinoma, head and neck squamous cancers, gastric adenocarcinoma, urothelial carcinoma, and mismatch repair-deficient/microsatellite instability-high solid tumors [3, 4••, 5]. ICIs have been shown to improve outcomes and overall survival (OS) for oncology patients [6–8]. Many ICIs are currently in development, as the indications for these agents continue to expand. See Table 1 for a list of ICIs currently used in oncology.

ICIs work by inhibiting checkpoints, which results in widespread amplification of the immune response. Since this augmentation in the T-cell response is not tumor-specific, there is concern that this may lead to autoimmune manifestations or immunotoxicities, as normal tissue is often affected [9]. These immunotoxicities are also known as immune-related adverse events (irAEs). The clinical spectrum of irAEs is wide, with the potential to affect virtually any organ. The gastrointestinal tract is one of the most commonly affected systems and is often associated with the most serious irAEs [10, 11]. Presentations range from self-limiting diarrhea to severe, life-threatening immune-mediated colitis (IMC) [6, 10, 11, 12•, 13].

As indications for ICIs continue to grow, guidelines for the management of irAEs are needed. Since irAEs are essentially autoimmune diseases, we typically approach management with immunosuppression using corticosteroids or biologic medications (i.e., infliximab or vedolizumab) [1•]. The aims of this review are to summarize current knowledge regarding IMC and provide an overview of the management of this disease process.

Immune-related adverse events predict favorable response

Interestingly, development of irAEs is actually associated with increased efficacy of the ICI and improved oncologic outcomes [1•, 14–21]. Haratani and colleagues showed that the median progression-free survival was 9.2 months (95% CI, 4.4 to not reached) in those who developed irAEs versus 4.8 months (95% CI, 3.0 to 7.5) in those who did not develop irAEs. Moreover, multivariable analysis revealed that irAEs were positively associated with survival outcome [18].

Diarrhea is the most common gastrointestinal irAE and is an independent predictor of improved survival regardless of its related treatment [1•]. A study of

Table 1. **Immune checkpoint inhibitors**

Anti-CTLA-4
Ipilimumab
Tremelimumab*
Anti-PD-1
Pembrolizumab
Nivolumab
Cemiplimab
Pidilizumab*
Anti-PD-L1
Atezolizumab
Avelumab
Durvalumab
*Currently not FDA approved

39 patients who developed enterocolitis had significantly higher tumor response rates (36% in multiple myeloma, 35% in renal cell carcinoma) than those who did not experience this irAE (11% in multiple myeloma and 3% in renal cell carcinoma) [15]. However, another study of 298 patients with melanoma treated with ipilimumab found no improvement in OS in those who experienced any irAE compared with those who did not [22]. Another study also demonstrated that increased toxicity did not appear to correlate with improved response rates [23].

Epidemiology

Incidence

Incidence—immune-related adverse events overall

Studies report an incidence as high as 90% for any grade irAEs due to ICI monotherapy [6, 24]. A meta-analysis indicates an incidence of 72% (95% CI, 65–79%) associated with CTLA-4 blockade [25] and 15 to 50% in PD-1 or PD-L1 blockade [17, 26–28].

Incidence and severity of irAEs is higher in patients on anti-CTLA-4/anti-PD-1 combination therapy (44%) than in those receiving anti-CTLA-4 (23–33%) or anti-PD-1 (≤19%) monotherapy. Generally, the proportion of patients experiencing high-grade symptoms is greater with anti-CTLA-4 than anti-PD-1/anti-PD-L1 agents [2, 29, 30].

There are discordant studies on whether higher doses of these ICI agents lead to greater toxicities. An association is seen in CTLA-4 blockade, in which a greater toxicity was noted at higher doses with agents such as ipilimumab [6, 15, 24, 31, 32]. In contrast, another study showed no increase in endoscopic ulcerations or the need for immunosuppression in patients who received higher doses of anti-CTLA-4 agents [33•]. This dose–toxicity relationship is not seen with anti-PD-1 or anti-PD-L1 therapy [34, 35].

Incidence—gastrointestinal immune-related adverse events

Diarrhea is a common irAE in immunotherapy with an incidence of 35% for anti-CTLA-4 agents, 20% for anti-PD-1 agents, and 44% for combination therapy [29, 36–38]. Gupta and colleagues noted watery diarrhea in 27–54% of those on anti-CTLA-4 therapy, such as ipilimumab and tremelimumab, with symptoms occurring within days to weeks of therapy initiation [39].

In a study of 198 patients with metastatic melanoma or renal cell carcinoma treated with CTLA-4 blocker ipilimumab, 21% developed enterocolitis, making it the most common major toxicity [15]. Gupta and colleagues found that diffuse acute and chronic colitis was the most common finding on endoscopy (8–22%) [39]. In a meta-analysis, the incidence of severe IMC was 9.1% with CTLA-4 monotherapy, 1.3% with anti-PD-1/anti-PD-L1 therapy, and 13.6% with combined therapy [40]. Incidence of IMC in anti-CTLA-4 treatment was noted to be approximately 4 to 5% [36, 41, 42] and 1 to 4% in anti-PD-1 and anti-PD-L1 therapy [17, 20, 21, 43, 44].

Diarrhea and colitis have been found to be the most common reasons for ICI therapy discontinuation [22, 29]. The prevalence of gastrointestinal irAEs differed, being less common in anti-PD-1 or anti-PD-L1 compared to anti-CTLA-4 agents [2, 6, 17, 29].

Potential risk factors for immune-mediated colitis

Nonsteroidal anti-inflammatory drugs

Marthey and colleagues demonstrated that among the 35 study participants who developed IMC, nonsteroidal anti-inflammatory drugs (NSAIDS) were more frequently used in those who developed enterocolitis than in those who did not (31 vs 5%, *p*=0.003) [33•]. This is similar to inflammatory bowel disease (IBD) and the association of NSAIDS with increased risk for IBD flare [45].

Medical history of autoimmune disease

Patients who have active underlying autoimmune disease are at risk for worsening of their autoimmune diseases while on ICI immunotherapy. In one study of patients with NSCLC on ICI immunotherapy, immunosuppression was required in 54% with rheumatoid arthritis, 38% with psoriasis, and 100% with polymyalgia rheumatic, Sjogren's syndrome, or immune thrombocytopenic purpura [46]. Two of the six patients with ulcerative colitis (UC) or Crohn's disease (CD) had ipilimumab-induced colitis or relapse of their IBD [47]. Very few data are available on the risk of IMC in patients with underlying IBD, as it is difficult to differentiate the two entities.

Medical history of immune-related adverse events

A few studies have shown that those who have had irAEs with one ICI agent are at increased risk for developing irAEs following initiation of an alternate ICI [23, 46]. Conversely, other studies have shown that patients with significant diarrhea or IMC during ipilimumab treatment have subsequently been treated with anti-PD-1 or anti-PD-L1 immunotherapy without developing recurrence of diarrhea or IMC [2, 42].

Combination therapy with two immune checkpoint inhibitors

In the treatment of metastatic melanoma, studies show that combination therapy with an anti-PD-1 and an anti-CTLA-4 agent results in longer patient OS [48]. As previously described, the incidence of irAEs on combination therapy is higher than in those on monotherapy [29, 48–50]. Although irAEs have been known to develop in the first few weeks or months of immunotherapy, those on combination therapy may be at risk of developing irAEs over a longer period of time [22]. Patients treated with combination CTLA-4 and PD-1 blockade develop more frequent and severe toxicities characteristic of both single agents, but do not appear to develop any irAEs that are unique to combination therapy [51].

Sequential therapy

Two case series report prolonged, difficult-to -treat IMC in patients who were treated with CTLA-4 blockade after anti-PD-1 antibody treatment [52, 53]. This was also seen in a subsequent study, where over one third of patients experienced IMC when treated with anti-PD-1 therapy followed by ipilimumab [23].

Table 2. Immune checkpoint inhibitor severity from the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0)

	Diarrhea	Colitis
Grade 1	<4 stools/day over baseline	Asymptomatic
Grade 2	4–6 stools/day over baseline	Abdominal pain, blood, and/or mucus in stool
Grade 3	≥7 stools/day over baseline	Severe abdominal pain, fever, and/or peritoneal signs
Grade 4	Life-threatening – Hemodynamics – Electrolyte abnormalities	Life-threatening – Perforation – Ischemia – Necrosis – Bleeding – Toxic megacolon
Grade 5	Death	Death

Adapted from the Common Terminology Criteria for Adverse Events version 5.0 from the National Cancer Institute [86]

Diagnosis

Clinical presentation

GI symptoms are less common with nivolumab than ipilimumab [29], possibly because PD-1 or PD-L1 seems to play less of a role in gut homeostasis than CTLA-4 [24, 29, 36, 54].

In those with IMC, the most common presenting symptoms are diarrhea (92%), abdominal pain (82%), hematochezia (64%), fever (46%), and vomiting (36%) [33•]. The median weight loss is approximately 8% of total body weight [33•]. The rate of bowel perforation is less than 1% and is considered uncommon [36, 54].

Onset of symptoms can occur at any point during the treatment course of anti-CTLA-4 immunotherapy, but frequently occur between the second and third doses [9, 15, 25, 55]. Colitis related to anti-PD-1/PD-L1 immunotherapy can also present at any point in the course, and some patients present even years into therapy, raising the hypothesis of ICI therapy being a potential trigger for underlying IBD [10].

Lord and colleagues demonstrated that symptoms may persist for several months after the last ICI dose. They also noted that the length of symptoms exceeded 130 days in two of their patients, which is greater than ten times the 12.5-day half-life of ipilimumab. This suggests that ICI therapy has a long-term effect on the immune system rather than checkpoint inhibition in the immune cascade simply at the time of treatment [55].

Case studies have also reported pancreatitis, hepatotoxicity, gastritis, and celiac disease due to ICIs [9, 56–58].

Grading

Classification and degree of severity are most commonly based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [86]. Unfortunately, this grading is arbitrary, as it is based on patient recall of symptoms and not on objective assessment of disease

activity. Consequently, it does not necessarily reflect the severity of the immunotoxicity [22]. Finally, there is poor correlation between grade of diarrhea and endoscopic or histological features for severity [16, 38]. See Table 2 for the CTCAE grading system.

Endoscopic findings

Since there is poor correlation between grade of diarrhea and endoscopic or histological features for severity, endoscopic evaluation should be strongly considered in those with symptoms more severe than CTCAE grade 1 diarrhea [16, 38]. In fact, the gold standard for diagnosis of IMC is endoscopy to better evaluate the mucosal extent and severity of disease. A colonoscopy with terminal ileum intubation, radiologic cross-sectional imaging, and/or video capsule endoscopy may be needed if isolated enteritis is suspected, as sometimes seen in anti-PD-1/anti-PD-L1 immunotherapy [33●].

Mild colitis is the most common finding in the colon and presents with diarrhea, affecting nearly half of the patients on high dose or combination therapy [24, 29, 36, 54]. Severe colitis occurs less frequently, but can be life-threatening [24, 29, 36, 54]. Many of the endoscopic and histologic features of IMC are similar to features seen in IBD [41]. Ipilimumab-induced colitis most closely resembles ulcerative pancolitis, which is seen in 66% of patients with IMC [33●]. Inflammation presents endoscopically as diffuse erythema, friability, shallow ulcerations, and edematous walls from cecum to anus [33●]. In contrast, segmental disease, as is often found in Crohn's disease, is less common and noted in 35% of individuals with IMC [33●]. Stricturing or fistulizing disease that is associated with Crohn's disease is not typically seen with IMC. Although most patients develop colitis alone, approximately a quarter of patients with colonic involvement also have diffuse enteritis [15].

In studies that evaluated anti-CTLA-4–associated enterocolitis, the rectum and sigmoid were involved 97% of the time [33●]. Therefore, a flexible sigmoidoscopy may suffice as the diagnostic tool in the vast majority of cases and a full colonoscopy may not be needed [33●, 59].

Those with ulcerations on initial endoscopy had a significantly higher rate of high-grade diarrhea than those without ulcers (100 vs 79%, p=0.033) [16]. There is no specific grading scale used for the endoscopic findings in IMC, but the Mayo endoscopic score for ulcerative colitis or the Simple Endoscopic Score for Crohn's disease (SES-CD) may be used [38].

A relatively high frequency of patients treated with PD-1/PD-L1 blockade develop low-grade diarrhea, but this rarely progresses to severe colitis [29, 43, 60–63]. Although severe colonic inflammation is much less common with PD-1/PD-L1 blockade than with anti-CTLA-4 immunotherapy, pneumonitis is more strongly associated with inhibition of the PD-1/PD-L1 pathway, emphasizing the different regulatory roles of these receptors within distinct tissues [41].

Histologic findings

IMC due to CTLA-4 inhibitors can have lymphocytic and/or neutrophilic infiltrates as well as increased numbers of apoptotic cells on histology [15, 33●, 38]. Neutrophilic inflammation was predominantly characterized by cryptitis with one-third showing crypt abscesses [15]. Lymphocytic predominance

demonstrating crypts and prominent eosinophils is less commonly seen. Although these can be present, it is less likely to see chronic architectural changes or granulomas. This is in contrast to IBD, in which chronic crypt architectural changes are often seen due to the chronicity of disease.

Notably, anti-PD-1/PD-L1 immunotherapy induces small intestinal and colonic inflammation that is clinically distinct from colitis induced by ipilimumab. Although these patients may develop low-grade diarrhea from isolated enteritis or colitis, histologic changes seem to resemble microscopic colitis [29, 43, 60–63].

Laboratory studies

Anemia, hypoalbuminemia, and elevated inflammatory markers, such as C-reactive protein and fecal calprotectin, are seen in IMC. As in IBD, these findings are nonspecific and may vary between individuals [33•]. Fecal calprotectin may be helpful in monitoring IMC disease activity [9, 64•, 65–67].

Radiologic studies

There are no distinct radiographic findings noted in IMC [68]. If there is concern for abscess or perforation, then cross-sectional imaging should be pursued [41]. If there is concern for enteritis, then enterography can be considered.

Management

There are no standardized guidelines in the management of IMC, but most recommendations are largely based on degree of severity. Infectious etiology for symptoms should be considered first. Stool studies for *Clostridium difficile* and other bacterial pathogens are recommended. Stool parasitic testing should be based on risk factors and provider discretion [10, 69]. Preliminary blood work including complete blood count, comprehensive metabolic panel, thyroid stimulating hormone, celiac disease serology, erythrocytes sedimentation rate, and C-reactive protein should be performed. Calprotectin may be helpful to monitor treatment response [9]. Other screening labs to obtain include hepatitis A and B serology, as well as tuberculosis testing, in preparation for possible initiation of biologic therapy if not responsive to corticosteroids.

For severe disease, corticosteroids should be used initially. If refractory to corticosteroids, biologic therapy with medications such as infliximab, an anti-tumor necrosis factor (TNF), or vedolizumab, an anti-integrin, should be considered. Wang and colleagues demonstrated that 56% of patients responded to corticosteroids alone, and 42% were corticosteroid-refractory but did respond to infliximab [16]. Approximately one third to two third of colitis cases have recurrence after corticosteroid taper or are refractory to corticosteroids [10, 15, 33•, 59]. Infliximab remains the most studied second-line agent [6, 70]. In most cases, only one to three doses [10, 15] are needed to improve symptoms. It is recommended that endoscopic evaluation with biopsies be performed to ensure mucosal and endoscopic healing.

In one study, patients treated with infliximab had a shorter time to symptom resolution. Resolution of diarrhea was 3 days in those who received corticosteroids followed by infliximab versus 9 days in those who received corticosteroids alone ($p<0.001$). In those with colitis, symptom recovery was 4 days in
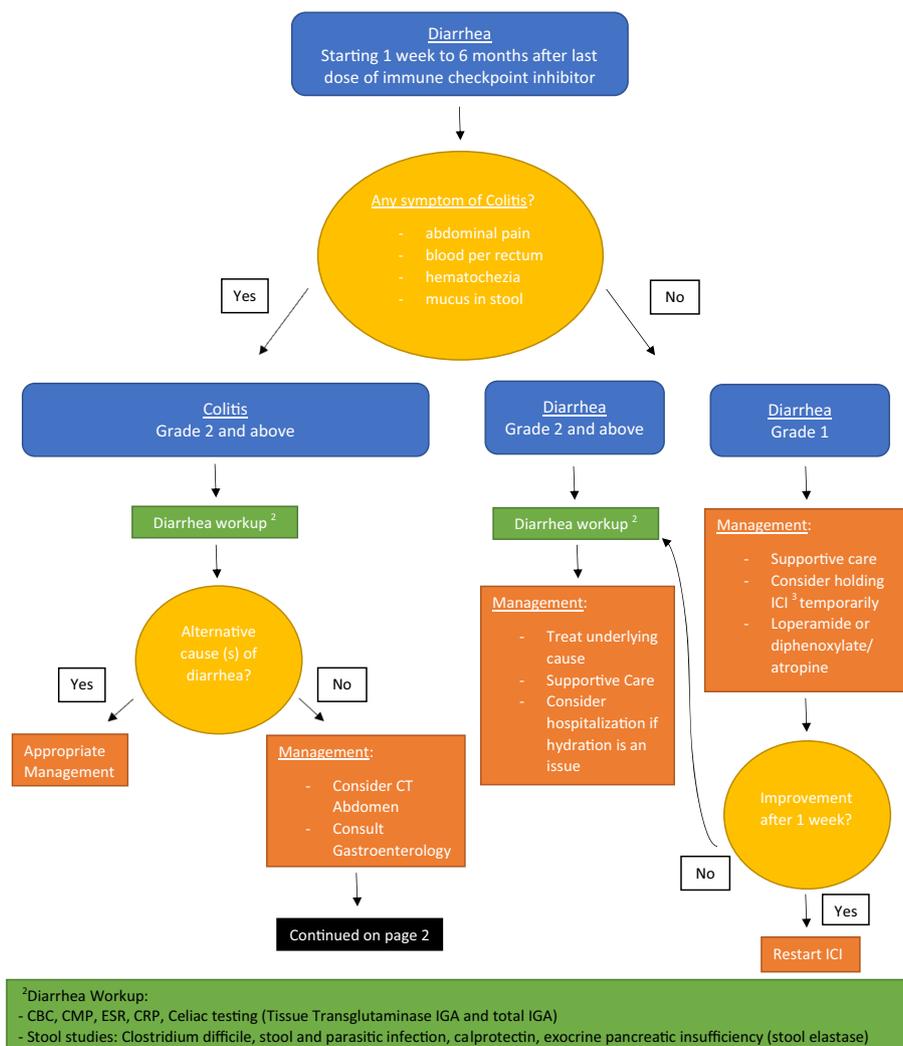
Fig. 1. Approach to diarrhea in the setting of immune checkpoint inhibitors based on MD Anderson Cancer Center's "Evaluation and Management of Suspected Immune-Mediated Colitis/Diarrhea" [73••].

those who received corticosteroids and infliximab and 13 days in those who received only corticosteroids (p<0.001). This was despite the infliximab group having more severe irAEs initially. There were also shortened length of hospital stay and improved quality of life, as well as greater avoidance of high-dose corticosteroids and their associated adverse effects [70]. Lastly, those who received two or less infusions of infliximab had less histologic remission and higher fecal calprotectin levels than those who received three or more infusions [71•].

Although current recommendations advise biologic use in patients who are refractory to corticosteroids, there are no recommendations to guide the use of
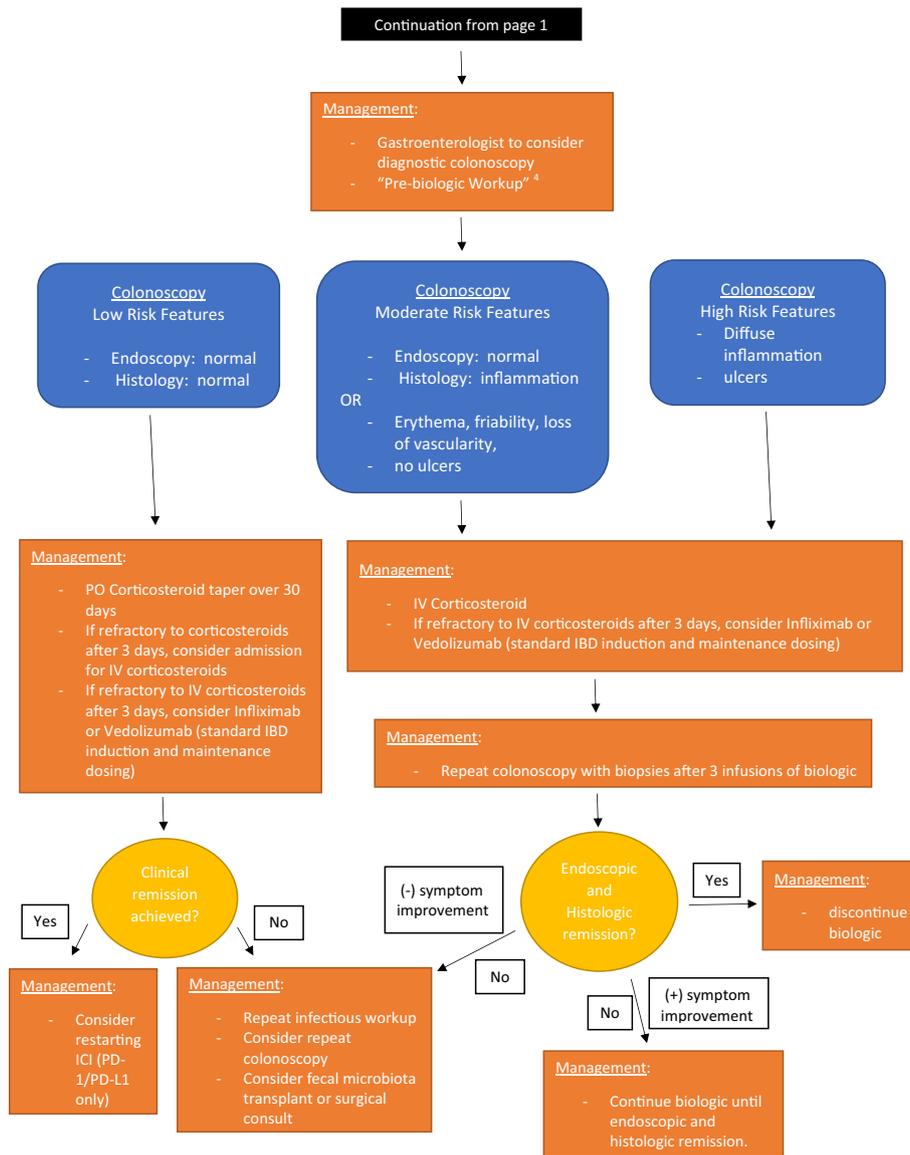
Continuation from page 1

Management:
- Gastroenterologist to consider diagnostic colonoscopy
- "Pre-biologic Workup" [4]

Colonoscopy
Low Risk Features
- Endoscopy: normal
- Histology: normal

Colonoscopy
Moderate Risk Features
- Endoscopy: normal
- Histology: inflammation
OR
- Erythema, friability, loss of vascularity,
- no ulcers

Colonoscopy
High Risk Features
- Diffuse inflammation
- ulcers

Management:
- PO Corticosteroid taper over 30 days
- If refractory to corticosteroids after 3 days, consider admission for IV corticosteroids
- If refractory to IV corticosteroids after 3 days, consider Infliximab or Vedolizumab (standard IBD induction and maintenance dosing)

Management:
- IV Corticosteroid
- If refractory to IV corticosteroids after 3 days, consider Infliximab or Vedolizumab (standard IBD induction and maintenance dosing)

Management:
- Repeat colonoscopy with biopsies after 3 infusions of biologic

Clinical remission achieved?
Yes   No

(-) symptom improvement

Endoscopic and Histologic remission?
Yes
No

(+) symptom improvement
No

Management:
- discontinue biologic

Management:
- Consider restarting ICI (PD-1/PD-L1 only)

Management:
- Repeat infectious workup
- Consider repeat colonoscopy
- Consider fecal microbiota transplant or surgical consult

Management:
- Continue biologic until endoscopic and histologic remission.

Fig. 1. (continued)

the biologic once it is initiated [4••, 6, 10, 72]. See Fig. 1 for a basic approach to diarrhea and IMC modified from hospital guidelines developed at MD Anderson Cancer Center [73••].

The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines also recommend to first determine the severity of the disease using CTCAE v 5.0 (see Table 2) [4••, 86, 87••]. Symptomatic treatment with anti-diarrheal medications is recommended for grade 1. Treatment with ICI can typically be continued. Careful monitoring and supportive care is recommended and the IMC is usually self-limiting.

If the patient has a grade 2 toxicity, ASCO recommends that the ICI be held until symptoms improve to grade 1 or less. One can also consider permanently

discontinuing anti-CTLA-4 agent and starting anti-PD-1 or anti-PD-L1 therapy if the patient's condition improves off of an ICI. A gastroenterology consult should be placed for further diagnosis and management. A flexible sigmoidoscopy or colonoscopy and/or esophagogastroduodenoscopy may be pursued. Immunosuppressive maintenance with 1 mg/kg/day of prednisone (or equivalent) may be initiated. A long taper is recommended over 4–6 weeks once symptoms have improved to a grade 1 or less [4••, 6, 9].

For grade 3 toxicities, permanently discontinuing anti-CTLA-4 agents is recommended. The patient may require medical attention for treatment of dehydration or any electrolyte imbalances. Corticosteroids should be initiated (initial dose of 1 to 2 mg/kg/day prednisone or equivalent). If symptoms persist≥3 to 5 days or recur after initial improvement, intravenous corticosteroids or biologic therapy with infliximab may be initiated. A repeat colonoscopy in some cases may be indicated, particularly to rule out concomitant opportunistic infections to treatment refractory disease [4••, 6, 9, 10, 22, 69]. If symptoms recover to grade 1 or less, patients may be started on anti-PD-1/anti-PD-L1 agents if indicated and infliximab discontinued.

For grade 4 toxicities, the ICI treatment should be permanently discontinued. The patient may require a hospital admission to closely monitor and treat the diarrhea and its complications. Gastroenterology consultation is needed to further guide management. Intravenous corticosteroids should be administered and not changed to oral formulations until symptoms start to improve. It is recommended that infliximab 5–10 mg/kg therapy be initiated and continued in patients who do not respond to corticosteroids within 2–3 days. Endoscopy is recommended for refractory or severe illness [9].

Response to therapy

In anti-CTLA-4 enterocolitis, 37% of the 39 patients achieved complete remission on corticosteroids. Of the 12 patients who required infliximab, ten (83%) responded [33•].

Overall, one third to two thirds of patients either do not respond to high-dose intravenous corticosteroids or have a relapse requiring an increase in the corticosteroid dosage during the course of steroid tapering [5, 7]. These patients usually have an excellent response to infliximab (dose 5 mg/kg) [10, 15, 22, 33•, 59, 74].

It is recommended to assess for endoscopic and histologic remission and not base decision-making on clinical symptoms alone, as there is a known discrepancy between symptoms and mucosal healing, as also seen in IBD [71•].

Although biologic drug trough levels for assessment of therapeutic drug monitoring can be used to assist in decision-making, target drug goal levels are not well understood in IMC. However, if adequate drug levels cannot be reached and the patient has not achieved a response, switch in biologic class of therapy to an alternative mechanism of action should be considered.

Refractory cases

Occasionally, there will be patients who are refractory to medical therapies to treat IMC, including both high-dose corticosteroids or infliximab. There are

currently no predictors for response. It is possible that these patients have underlying or unmasked IBD that has been triggered by the ICI [9].

History of IBD

Those patients who have a history of IBD, which was quiescent at the time of ICI initiation, may be more refractory to treatment if they develop IMC. ICIs should be avoided in patients with active IBD in the setting of malignancy [47]. Very few studies are available on the risk of IMC in patients with CD or UC, as these entities are difficult to differentiate.

Infections

As in IBD, infections such as CMV and HSV should be excluded for refractory disease. Endoscopy with biopsies is the recommended approach.

Vedolizumab

Vedolizumab, an anti-integrin, is being explored as an effective alternative to anti-TNF therapy in the setting of IMC, as either a first-line biologic after corticosteroid failure or as a second-line biologic in anti-TNF primary nonre-sponders [64•]. Vedolizumab is gut-selective and may have a better safety profile [60, 64•, 74–76].

Vedolizumab can also be considered in the treatment of IMC in patients with a contraindication to anti-TNF agents, such as those with New York Heart Association (NYHA) Functional Classification greater than 3, latent tuberculo-sis, or multiple sclerosis [64•].

Abu-Sbeih and colleagues [64•] compared the response in patients who failed both corticosteroids and infliximab before trialing vedolizumab versus those who failed just corticosteroids prior to initiation of vedolizumab. There was a shorter mean duration of corticosteroid use in the second group (85 vs 131 days). Vedolizumab led to clinical remission in 84% patients with corticosteroid-refractory ICI colitis and endoscopic remission in 54% of pa-tients. The mean duration of improvement of symptoms was 5 days after the initial dose of vedolizumab. In a case series of seven patients, all but one patient experienced corticosteroid-free IMC remission with normalized fecal calprotectin after vedolizumab therapy. This was achieved after a median of 56 days from vedolizumab initiation, and no adverse effects from biologic treatment were noted [75].

As previously demonstrated among IBD patients, a better response rate is seen in anti-TNF naïve patients treated with vedolizumab as first-line therapy. Those receiving a longer duration of corticosteroid therapy were also found to have lower responses to vedolizumab [64•].

Fecal microbiota transplant

There is increased bacterial diversity of the microbiome in those who did not develop IMC with ipilimumab immunotherapy [77–80]. Studies are currently under investigation for the potential role of fecal microbiota transplant (FMT) in IMC. In one case series, FMT performed on biologic-refractory IMC patients did have clinical, endoscopic, and histologic improvement [81].

Colectomy

In a study of 39 patients with anti-CTLA-4-mediated colitis, six patients required colectomy (five due to perforation and one due to toxic megacolon) [33•]. If surgery is needed, subtotal colectomy, as opposed to a segmental colectomy, is recommended as pancolitis is the most common presentation [33•].

Prophylaxis

Prophylactic treatment with corticosteroids, including budesonide, on patients undergoing treatment with ICIs did not prevent the development of diarrhea or colitis. Furthermore, it is not known if taking corticosteroids or infliximab concomitantly with the ICI will prevent IMC [33•, 42].

Prognosis/follow-up

Recurrence

During a mean follow-up of 19 months, 19 of 53 patients (36%) experienced recurrent diarrhea despite successful initial treatment with immunosuppression. Three were successfully treated with anti-diarrheal medications, ten needed a repeat course of corticosteroids, and six ultimately required infliximab maintenance therapy. The initial grade of diarrhea or colitis, presence of endoscopic or histologic inflammation, requirement of infliximab for initial treatment, or the duration of corticosteroid therapy was not associated with recurrence [16]. Based on these findings, it is not possible to predict which patients will experience recurrence and close follow-up is recommended even when a patient is initially in remission.

Immunosuppression and efficacy

There is a concern for tumor progression or attenuated response to ICIs if immunosuppression is needed with corticosteroids or biologics in the treatment of irAEs. Immunosuppressants work to suppress T-cell activation, which in theory, could negate the benefits of checkpoint inhibition. However, published findings do not support this theory with nivolumab, ipilimumab, or corticosteroids [14, 15, 17, 22, 82–85]. Of 576 patients with advanced melanoma evaluated in four clinical trials, Weber and colleagues found that in the 24% who received immunosuppressive therapy for irAEs, there was no significant difference in objective treatment response rates or the rates and effectiveness of the anti-cancer tumor response [17].

Those who develop severe irAEs do trend toward increased survival. However, the possibility of increased overall survival with corticosteroid-sparing treatments is unknown. No differences were found in overall survival between patients who received steroids without infliximab and those who received steroids with infliximab (p=0.768) [1•]. However, available studies investigating the effect of corticosteroid sparing treatments on overall survival are sparse.

Question of progression to inflammatory bowel disease

Studies have shown persistence of endoscopic and histologic inflammation several months after onset of treatment for IMC, with or without clinical symptoms. This observation stands true in patients with IBD, where it takes

longer for histologic and endoscopic features to resolve when compared with clinical symptoms alone. It is unclear if this signifies a progression toward chronic inflammatory bowel disease [33•, 64•].

Reintroduction of checkpoint inhibitors after treatment for immune-mediated colitis

Marthey and colleagues [33•] noted that four of the six patients who had an additional infusion of ipilimumab after IMC remission experienced a relapse. Three of these four patients required a repeat corticosteroid course with eventual achievement of remission. The fourth patient was refractory to the corticosteroid course and required an infliximab infusion. There is a high risk of relapse in those with IMC history who undergo reintroduction of a checkpoint inhibitor [33•]. Risks and benefits of retreatment with anti-CTLA-4 medications should therefore be closely weighed with the patient and oncology team.

Infection risk with immunosuppression

In a retrospective, single-center study, 37% of the 79 patients developed IMC or diarrhea and were given corticosteroids with or without biologic therapy. Duration of corticosteroid use in patients who developed infections was longer than in those who did not develop infections (80.4 vs 46.7 days; p=0.063). The median length of steroid treatment in patients who developed an infection was 60 days and only 34 days in patients who did not. No other significant differences in terms of cancer stage, malignancy type, ICI agent, diarrhea grade, or colitis grade were observed between patients who did or did not develop infections [1•]. These findings again suggest early initiation of corticosteroid-sparing treatment.

Conclusion

ICIs have revolutionized the field of oncology and have become the standard of care for a wide range of malignancies. Despite important clinical benefits, these medications can cause irAEs, including IMC, which closely resembles and appears to be an accelerated form of IBD. To further prevent complications, prompt recognition of corticosteroid failure and subsequent initiation of biologics is imperative. Infliximab is most commonly recommended, but early studies show promise with vedolizumab therapy as well. Resumption of ICIs should be approached cautiously, as there is a high likelihood of relapse. A multidisciplinary group consisting of gastroenterologists and oncologists is necessary to provide comprehensive care and to ensure a methodical approach to this emerging disease spectrum.

Author contributions

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- •   Of importance
- ••   Of major importance

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