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INFLAMMATORY BOWEL DISEASE (B COHEN, SECTION EDITOR)

Update on Immune Checkpoint Inhibitor Enterocolitis

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Abstract

Purpose of Review Immune checkpoint inhibitor (ICI) therapy revolutionized the treatment of multiple solid and hematologic malignancies. Yet, with it came profound inflammatory toxicities that mimic autoimmune diseases, termed immune-related adverse events (irAEs). Prominent among these is gastrointestinal inflammation, including a spectrum of gastritis, enteritis, and colitis. Here we synthesize an approach to immune checkpoint related enterocolitis (irEC) – including diagnostics and therapeutics – underpinned by new insights into the mechanism behind these phenomena.

Recent Findings This review presents updated insights on how to approach irEC, including novel approaches to selective immunosuppressive therapy, the role of fecal microbiota transplant, and the underlying cellular mechanisms of irEC.

Summary This review provides an update on irEC diagnosis and therapy, with considerations of new therapies and special patient populations. The field of gastrointestinal irAEs requires additional investigation, which will ultimately provide the tools required for patients to continue to receive life-saving ICI therapy.

Keywords CTLA-4 · PD-1 · PD-L1 · Immune-checkpoint inhibitor · Immune-related adverse event · Toxicity

Abbreviations

AGA	American Gastroenterological Association
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
GI	Gastrointestinal
IBD	Inflammatory bowel disease
ICI	Immune checkpoint inhibitor
IFNγ	Interferon-γ
IL	Interleukin
irAE	Immune-related adverse event
irEC	Immune-related enterocolitis
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
SIT	Selective immune therapy
TNFα	Tumor necrosis factor-α
TRMs	Tissue-resident memory T cells

Introduction

Immune checkpoint inhibitor (ICI) therapy has revolutionized the treatment of cancer, including treatment of both solid and hematologic malignancies [1, 2]. These monoclonal antibodies primarily target two immune regulatory pathways: cytotoxic T lymphocyte-associated protein (CTLA)-4 and programmed death (PD)-1 or its ligand (PD-L1) [1, 2]. Therapeutically, this leverages a powerful antitumor immune response by disabling the physiologic "breaks" on T cell responses. ICIs have shown impressive responses in both solid (e.g. melanoma [3, 4], pulmonary [5–8], and urothelial [9–11]) and hematologic (e.g. Hodgkin's Lymphoma [12, 13]) malignancies.

Yet, ICI therapy also disables the critical peripheral tolerance mechanisms mediated through these pathways. This can lead to loss of T cell tolerance for self-antigens and

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commensal bacterial antigens, as well as B-cell activation and the production of auto-antibodies [14–16]. Loss of tolerance produces a wide variety of inflammatory toxicities that are collectively referred to as immune-related adverse events (irAEs) [17–19].

Although the impact of irAEs spans the majority of organ systems, they most significantly impact barrier organs, including the integumentary, pulmonary, and gastrointestinal (GI) systems [20–22]. IrAEs are common; the great majority of patients who receive dual immunotherapy (blocking CTLA-4 and PD-1) develop an irAE, and approximately half of patients develop a treatment-limiting irAE. Immune checkpoint related enterocolitis (irEC) occurs in up to 40% of patients on dual ICI therapy [20, 23•]. Severe colitis is less common, impacting 2–5% of patients on PD-(L)1 inhibitors and up to 10% of patients on single agent CTLA-4 inhibitors [23•, 24•]. Dual therapy confers the highest risk of severe gastrointestinal toxicities with 15–20% of patients developing severe colitis [23•, 25, 26•]. Interestingly, while colitis is the most common cause of gastrointestinal symptoms related to ICI use, one recent pathology assessment of patients on ICI therapy revealed that the most common site of mucosal inflammation is the stomach [27]. Luminal disease is also not the only common irAE affecting the gastrointestinal system, with ICI toxicity also occurring in the liver, biliary tree, gallbladder, and pancreas [22, 23•, 24•, 26•, 28••, 29, 30].

Diagnostics

When a patient being treated with ICIs presents with gastrointestinal symptoms, we pursue a broad differential diagnosis to eliminate concurrent and confounding etiologies. This both ensures proper diagnosis and decreases the risk of secondary harm during both ICI and irAE therapy. Society guidelines recommend eliminating common diagnoses, including infection (*C difficile*, CMV, EBV, ova and parasites), endocrinologic causes (thyroid-stimulating hormone), pancreatic insufficiency (stool elastase), and the role of non-ICI medications (senna, polyethylene glycol, magnesium-containing compounds, etc.) [17–19]. Medication review ought to include additional oncologic therapies, as several (including tyrosine kinase inhibitors) [31] may cause diarrhea alone. These medications may require being held prior to more advanced diagnostics.

Further, ICI-related gastrointestinal disease includes standard ICI-related enterocolitis, ICI-related microscopic colitis (lymphocytic inflammation in the colon in the absence of macroscopic signs of inflammation) [32••], and ICI-related celiac disease [33•]. Indeed, celiac disease is an important confounding diagnosis [33•, 34]. Patients may have either an underlying diagnosis of celiac disease that was previously missed or treatment related breach in tolerance leading to new celiac disease. Celiac disease may be identified in patients with suspected ICI toxicity by sending appropriate serum markers (TTG-IgA, total IgA) in addition to mucosal biopsies [33•].

If review of medications and other etiologies for diarrhea are inconclusive, or if symptoms are severe and persistent, patients may require additional investigation. Fecal calprotectin, fecal lactoferrin, and stool electrolyte testing may help identify non-inflammatory sources of diarrhea, including pancreatic insufficiency, endocrine abnormalities, and functional disorders. Fecal lactoferrin and calprotectin may help risk stratify patients for urgency of endoscopy [18]. Erythrocyte sedimentation rate, and c-reactive protein hold low sensitivity and specificity. This is due in part to competing pathologies related to malignancy and oncologic therapy, as well as the diagnostic overlap with other secondary conditions (e.g., infections or autoinflammatory diseases). Likewise, the value of trending these markers through treatment remains unclear [18].

The severity of gastrointestinal symptoms in the setting of ICI treatment is characterized by the Common Terminology Criteria for Adverse Events (CTCAE) grading system (which includes both criteria for diarrhea and enterocolitis) [35] and two endoscopic scoring tools, the Mayo Clinic Endoscopic Score which is adapted from use in ulcerative colitis, and an investigational scoring system developed by MD Anderson Cancer Center (MD Anderson Cancer Center Endoscopic Inflammation Grade). The CTCAE score for diarrhea includes five grades: (1) Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline, (2) Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL, (3) Increase of > = 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL, (4) Life-threatening consequences; urgent intervention indicated, and (5) Death. Likewise, the CTCAE score for enterocolitis also includes five grades: (1) Asymptomatic; clinical or diagnostic observations only; intervention not indicated, (2) Abdominal pain; mucus or blood in stool, (3) Severe or persistent abdominal pain; fever; ileus; peritoneal signs, (4) Life-threatening consequences; urgent intervention indicated, and (5) Death (Tables 1, 2, and 3).

While CTCAE is an effective clinical tool to classify patient symptoms and for trending response to therapy, the score does not correlate with endoscopic mucosal severity measures, nor does it predict response to enterocolitis therapy [19, 36••].

Definitive diagnosis of ICI enterocolitis requires endoscopic biopsy, though clinical diagnoses are commonly made in practice based on symptoms and the absence of competing etiologies. Nevertheless, among patients with

Table 1 Common terminology criteria for adverse events (version 5)—grading for gastrointestinal toxicity

Common terminology criteria for adverse events		
Grade	Features—Diarrhea	Features—Enterocolitis
1	Increase of < 4 stools per day over baseline Mild increase in ostomy output compared to baseline	Asymptomatic Clinical or diagnostic observations only Intervention not indicated
2	Increase of 4–6 stools per day over baseline Moderate increase in ostomy output compared to baseline Limiting instrumental ADL	Abdominal pain Mucus or blood in stool
3	Increase of > 7 stools per day over baseline Hospitalization indicated Severe increase in ostomy output compared to baseline Limiting self-care ADL	Severe or persistent abdominal pain Fever, ileus, and peritoneal signs
4	Life-threatening consequences Urgent intervention indicated	Life-threatening consequences Urgent intervention indicated
5	Death	Death

Table 2 Mayo clinic endoscopic scoring

Mayo endoscopic score	
Grade	Endoscopic appearance
0	Normal
1	Erythema, mild friability
2	Marked erythema and friability, erosions
3	Spontaneous bleeding, mucosal ulcerations

suspected ICI enterocolitis, mucosal inflammation is only present in approximately 80% of cases [24•, 37]. When inflammation is present in the colon, more than 95% of patients have inflammation on left colon biopsy, thus flexible sigmoidoscopy is often appropriate to make a diagnosis and may be used in patients who are highest risk for colonoscopy [32••, 38]. Pancolitis is the most common presentation for luminal inflammation, and regional variability revealing various grades of disease may be present [39•]. Additionally, > 10% of patients have isolated upper GI inflammation (gastritis, gastroenteritis, or enteritis), suggesting that esophagogastroduodenoscopy (EGD) may be an important diagnostic test, especially for patients with severe presentations and site-specific symptoms [37].

As mentioned above, endoscopic severity is typically assessed using one of two systems, the Mayo Clinic Endoscopic Score and the MD Anderson Cancer Center Endoscopic Inflammation Grading Scale. The Mayo score assesses disease activity as, (0) normal or inactive – no endoscopic features, (1) mild – erythema, decreased vascular pattern, mild friability, (2) moderate – marked erythema, absent vascular pattern, friability, erosions, (3) severe – spontaneous bleeding, ulceration. The MD Anderson scale assesses endoscopic features as, (1) mild – normal endoscopy and normal histology, (2) moderate – normal colon appearance with pathology showing inflammation, small ulcer < 1 cm, shallow ulcer < 2 mm, and/or number of ulcers < 3, inflammation limited to the left colon only, non-ulcer inflammation, or (3) severe – large ulcer ≥ 1 cm, deep ulcer ≥ 2 mm, and/or number of ulcers ≥ 3, extensive inflammation beyond left colon.

Importantly, based on prior literature, up to 30% of patients with symptoms of ICI enterocolitis have no mucosal inflammation, and these patients often respond to colonic formulations of budesonide [32••]. Colonic ulceration and

Table 3 MD anderson cancer center endoscopic inflammation grading

MD Anderson cancer center endoscopic inflammation grading	
Disease activity	Endoscopic features
Mild	Normal endoscopy Normal histology
Moderate	Normal colon appearance with pathology showing inflammation, small ulcer < 1 cm, shallow ulcer < 2 mm, and/or number of ulcers < 3; inflammation limited to the left colon, non-ulcer inflammation
High	Large ulcer > 1 cm, deep ulcer > 2 mm, and/or number of ulcers > 3; extensive inflammation beyond left colon

severe mucosal inflammation more generally (Mayo Endoscopic Score 3) is the only established variable that predicts whether ICI enterocolitis will respond to initial treatment with systemic glucocorticoids. Likewise, biopsy may differentiate between variable types of colitis, including ICI microscopic colitis, ICI-related celiac disease, and standard ICI macroscopic colitis [36••, 37, 39•]. As each of these diagnoses leads to variable treatment strategies, tissue biopsy and histopathologic examination can play an important role guiding the management of irEC.

Retrospective analyses of cross-sectional imaging for classifying ICI enterocolitis have demonstrated limited utility. Both computed tomography (CT) and magnetic resonance imaging (MRI) have been reviewed on retrospective analyses, and neither provide conclusive diagnostic capability. CT sensitivity and specificity are both low and widely variable (53–85% and 75–78%, respectively) [40, 41]. This is due in part to the wide differential that is indistinguishable on imaging, including new malignancy, infection, ischemia, and bowel wall edema. Imaging is most useful in the setting of suspected extra-luminal complications such as perforation or abscess where management may differ substantially from standard irEC treatment [19].

Therapies

Mild symptoms, including diarrhea, are common during ICI therapy. This is typically self-limited and can be managed empirically. First line therapy includes oral hydration, bland diet (without lactose or caffeine), and anti-diarrheal agents (i.e., loperamide 2—4 mg q4hrs up to 16 mg per day) once infection has been excluded [19]. Symptoms ought to resolve in 7—10 days. For mild disease, ICI therapy may be continued [17, 18]. If symptoms persist or evolve to grade 2, endoscopic evaluation may help guide subsequent management [21, 22].

Patients with Mayo 0 (no endoscopic features of colitis) often respond to treatment with budesonide. Management typically includes oral budesonide 9 mg daily for a total of six weeks (if stopping ICI therapy) followed by a taper, or indefinite maintenance therapy (if continuing ICI therapy). Patients with microscopic colitis who have concurrent upper gastrointestinal disease may not respond to budesonide, as colonic budesonide formulations have low coverage of the small intestine. In this case, a trial of mesalamine (800 mg three times daily) may be appropriate.

For patients with Mayo 1 (erythema, decreased vascular pattern, mild friability) and Mayo 2 (marked erythema, absent vascular pattern, friability, erosions) endoscopic findings, first line therapy is steroid treatment. For patients tolerating oral nutrition (fluids and bland diet), without systemic symptoms (fever, hypotension), a trial oral glucocorticoid therapy with oral prednisone 0.5—2 mg/kg/day (or dose equivalent) is appropriate. Prednisone may be tapered by 10 mg every 5—7 days after symptoms improve.

For patients with Mayo Endoscopic Score 1–2 and systemic symptoms, treatment may need to be escalated to inpatient hospitalization for monitoring and intravenous steroids, although most patients do not have systemic symptoms and can be managed as outpatients. Mayo 1 disease with systemic symptoms is typically treated with methylprednisolone 0.5—1 mg/kg/day divided into two doses every 12 h. Mayo 2 disease or enteritis is typically treated with methylprednisolone 1—2 mg/kg/day, divided into two doses every 12 h. During a prolonged steroid therapy (> 15 mg/day for four weeks), patients should be treated with *Pneumocystis jeroveci* pneumonia prophylaxis. Use of steroids in ICI irAE is supported by observational clinical data [26•, 39•] and society guidelines [18]. Still, there exists a risk of dampening the antitumor response both through withholding ICI therapy and through the direct immunosuppressive effects of steroids [42, 43••, 44•].

Mayo Endoscopic Score 3 (spontaneous bleeding, ulceration) requires high dose intravenous steroid treatment and strong consideration for initiation of selective immune therapy (SIT). Patients with Mayo Endoscopic Score 1—2 who do not respond to steroid therapy should also be considered for SIT. First line SIT includes anti-tumor necrosis factor-α (TNFα) therapy with infliximab, at an initial dose of 5 mg/kg IV at weeks zero, two, and six. Patients with severe disease and/or hypoalbuminemia (< 2.5 g/dL), may be started on an initial dose of 10 mg/kg [17, 45–47], though this is not universal practice. Typically, response is seen over the first one to three days after initiation of therapy. Interestingly, preclinical work has also hypothesized that anti-TNFα use in the setting of ICI therapy may promote tumor regression by preventing immune escape via reducing activation-induced cell death of CD8 + tumor-infiltrating T cells [48••, 49].

As in inflammatory bowel disease (IBD), patients undergoing anti-TNFα therapy should be tested for latent Hepatitis B and tuberculosis. Relative contraindications include active uncontrolled infection, latent tuberculosis, demyelinating disease (optic neuritis, multiple sclerosis), severe heart failure and hematologic malignancy, though in practice most of these patients are still appropriate for infliximab use given the immediate life-threatening risk of irEC and the typically short duration of anti-TNFα therapy.

Infliximab therapy is widely considered safe, with studies indicating that irEC may be managed with anti-TNFα therapy without impacting tumor response and without dose-limiting toxic effects [36••, 50]; additional studies have affirmed these findings in patients with ovarian and renal cell carcinoma [51, 52]. Notably, this seemingly contradicts work using data from the Dutch Melanoma Treatment Registry, which found that in patients on PD-1 and/or

CTLA-4 blockade, those with severe ICI toxicity had prolonged survival and that patients who received anti-TNFα had decreased survival versus those managed on steroids alone (overall survival 17 vs 27 months) [53•]. Yet, this study did not include information on the specific irAE diagnosis and was agnostic to the total steroid dose used. Patients on a brief or low-dose steroid course are likely included in the "steroid alone" category, thus biasing toward a healthier cohort with lower steroid exposure.

In the event that a patient is non-responsive to infliximab or has a relative contraindication to anti-TNFα therapy, one may consider blocking gut-specific integrin homing using the α4β7 inhibitor, vedolizumab. Induction therapy is administered at 300 mg IV at weeks zero, two, and six [54••]. Vedolizumab therapy has been studied in patients after failure of both steroids or steroids and infliximab therapy (9 of 28 patients total), including in patients with grade 3–4 colitis (13 patients) [55]. After approximately 15 weeks of monitoring, 86% of patients achieved durable clinical remission, including 67% of patients who did not respond to steroids and infliximab combination therapy [55]. No prospective data are currently available comparing infliximab to vedolizumab as first line therapy for irEC, and both treatment strategies are reasonable as initial management for steroid-refractory irEC. Encouragingly, one two-center retrospective observational study of 184 patients (94 infliximab, 62 vedolizumab, and 28 sequentially treated patients), revealed similar clinical remission in the two single-treatment groups (88% vs 89%), with vedolizumab having slightly fewer hospitalizations (16% vs 28%), shorter hospitalizations (10.5 days vs 13.5 days), and shorter steroid use (35 vs 50 days), despite longer time to clinical response (17.5 vs 13 days) [56•]. Because of the apparent slower response rate of vedolizumab, infliximab is generally the preferred agent in patients with severe mucosal disease or debilitating symptoms, though the decision to select one of the two agents should ultimately be an interdisciplinary one based on patient specific factors.

Regardless of the specific drug, SIT (infliximab or vedolizumab) ought to be used in patients with high-risk endoscopic features and failure to have a symptomatic response within three days of initiating high dose glucocorticoid therapy. Upfront treatment with SIT may be appropriate in the most severe mucosal disease, though this question has not been adequately addressed in the literature. In addition, SIT should be used in any patient with a partial response to systemic glucocorticoids after a week on therapy, or any patient who has recurrent symptoms during the glucocorticoid taper.

Further, as discussed above, irEC may also present as microscopic colitis or ICI-related celiac disease. Microscopic colitis (collagenous or lymphocytic) may present with a broad spectrum of symptoms, similar to macroscopic colitis. Management typically includes oral colonic formulations of budesonide 9 mg daily for six weeks followed by a taper (if stopping ICI therapy), or indefinite maintenance therapy (if continuing ICI therapy) [32••, 57–59]. Patients often require a slow taper from 9 to 6 mg (for two weeks) to 3 mg (for two weeks), with close monitoring of symptoms and CTCAE diarrhea scale to determine the rate of tapering. In those who do not respond to colonic-formulated budesonide, prednisone is a reasonable alternative. Importantly, while budesonide therapy is effective in microscopic colitis, it has been shown to be ineffective in ICI-mediated macroscopic colitis and ought to be avoided [28••].

ICI-related celiac disease is another important subpopulation of patients with ICI gastrointestinal toxicity, whose disease may present with symptoms that overlap with irEC including life threatening presentations [34]. ICI-related celiac disease should be treated with a gluten free diet. A subset of patients with severe disease also require immunosuppression with steroids [60–62] or SIT [34, 63, 64]. Likewise, patients may require nutrient repletion, including iron, vitamins, and minerals [33•]. After the acute disease has resolved, patients with ICI-related celiac disease should be considered for typical celiac-related screening, including evaluation for iron absorption, vitamin B12, folate, vitamin D level, and bone density testing [65].

Immune Mechanisms of irEC and Refractory Disease

The molecular and cellular drivers of irEC are only beginning to be fully characterized. Detailed analyses of irEC have showed a marked expansion of CD8 + effector T cells that express both interferon-γ (IFNγ) and Granzyme B in patients treated with ipilimumab monotherapy, combination immunotherapy, and single agent PD-1 blockade [66••, 67•]. These cells are highly proliferative, consistent with the clinical observation of rapid colitis progression after the first symptoms of colitis are evident. Th1 type CD4 + T cells are also expanded though to a lesser extent, and multiple immune cell types show signatures consistent with IFNγ signaling through the JAK-STAT pathway. Consequently, JAK-STAT signaling downstream of IFNγ has been an attractive target for treatment of refractory irEC, though with some significant concern about interfering with antitumor responses given the abundant evidence for a central role for IFNγ in mediating antitumor immunity [66••].

The origin of these expanded CD8 + T cells appears to be the tissue resident memory pool of the colonic mucosa (TRMs) [67•]. This is based on TCR clonotype matching, RNA velocity analyses, and surface expression of CD103. The target of these expanded T cells is not yet clear, though the presence of shared TCRs with the TRMs suggests possible targets within the host microbiome,

providing some conceptual justification for strategies to treat refractory irEC through FMT and other technologies to manipulate the microbiome as discussed below.

Although the CD8 + colitis-associated T cells appear to originate in the colonic mucosa, the origin of the colitis-associated CD4 + T cells is unclear, and many of these cells express gut homing integrins, suggesting that they may enter the tissue from other peripheral sites, providing some mechanistic support for the efficacy of vedolizumab, and also potentially explaining why this therapy leads to slower responses. Further supporting this model, recent analyses have linked expanded memory CD4 + T cells in the circulation to increased risk for irAEs, including irEC [68, 69•].

The primary source of TNFα in irEC appears to be macrophages, which exhibit an inflammatory phenotype in irEC, producing a number of factors that likely propagate the disease including chemokines that can recruit additional T cells. How blockade of TNFα leads to resolution of colitis is not clear currently, but TNFα receptors are present on both the colitis-associated myeloid cells and on the expanded CD8 + T cells.

Given the endoscopic and pathologic similarities between irEC and IBD (Crohn's and ulcerative colitis), recent work analyzed the immune response in patient samples taken from patients with ICI and IBD. Comparing patients with irEC to IBD, samples derived from patients with irEC had increased proliferation of T cells, increased IFNγ, and relatively normal IL-17 expression; plasma B cells did not undergo IgA + to IgG + transition, as seen in inflammatory bowel disease [66••, 70, 71]. Understanding how these disease states differ will better allow us to tailor therapies aimed at the unique immune response mechanisms or irEC.

Several small clinical studies have examined alternative agents for refractory irEC. Ustekinumab, an antibody to the p40 subunit of interleukin (IL)-12 and 23, and tofacitinib, a JAK1/JAK3 inhibitor have both shown signs of efficacy in irEC. Case series have shown improvement in ICI enterocolitis with ustekinumab in two patients (one receiving anti-PD-1 and one receiving anti-PD-1 followed by anti-CTLA-4), after those cases were refractory to vedolizumab and infliximab/vedolizumab, respectively [72]. The mechanism of action of ustekinumab is potentially through interfering with IL-12 mediated differentiation of Th1 cells. One case report and an additional four-patient case series have revealed efficacy of JAK inhibition with tofacitinib in ICI enterocolitis refractory to both infliximab and vedolizumab treatment [73, 74••]. As discussed above, tofacitinib may provide durable responses due to inhibition of IFNγ signaling, which is a cardinal feature of irEC [66••, 67•]. Both of these therapies, however, are likely to interfere with important aspects of antitumor immunity and should be reserved for use in life-threatening cases of irEC.

While case series have shown the use of combination infliximab and vedolizumab in IBD [75–77], similar combination treatment has not undergone widespread study in irEC. Instead, patients have undergone stepwise progression in therapy (escalation from steroids to infliximab to vedolizumab to potentially another agent), rather than concurrent combined intervention, as discussed above. Given the recent small successes in combination treatment for IBD, future therapy may consider a similar approach in irEC.

Finally, fecal microbiota transplant has been evaluated in refractory ICI enterocolitis [78••]. This builds upon previous work that has suggested improvement in both *C. difficile* colitis and IBD after FMT [79], as well as work revealing variable gut microbiome in ICI responders vs non-responders and variable gut microbiome between patients who develop irEC and those who are unaffected [80–83]. Two patients underwent FMT of healthy donor stool. One patient was on combination PD-1/CTLA-4 blockade and had not achieved stable control of colitis with steroids, infliximab, and vedolizumab; the other received CTLA-4 blockade alone, followed by failure to control symptoms on combined steroids, infliximab, and vedolizumab. Both patients had complete resolution of symptoms, with reconstitution of the gut microbiome and a relative increase in the proportion of regulatory T cells within the colonic mucosa.

Powerful machine learning analyses have been used to investigate the link between the microbiome and overall response rate and progression-free survival of ICI therapy in a population of 175 patients [84]. While cohorts of bacteria were associated with responders, no single species applied across all studies. Indeed, additional work on the complex interplay between ICI therapy, the microbiome, and risk stratifying the efficacy of FMT in refractory colitis is needed.

Restarting ICI after Resolution of Colitis

The safest approach to restarting ICI therapy after resolution of irEC is currently unclear, as there exists a risk of disease recrudescence with reintroduction. While restarting ICI therapy may be safe with close clinical monitoring, few clinical tools exist to guide treatment strategy, and each patient ought to be considered independently. Guidelines suggest that patients with grade 4 irEC do not restart ICI therapy, and prospective data on safety are lacking. Mucosal severity is more likely a better measure of the risk of ICI reintroduction in patients with irEC than are CTCAE based symptom assessments.

Three broad approaches can be considered to ICI re-initiation: (1) restart the same ICI, (2) change ICI therapy, (3) add a selective immunosuppressive therapy. Alternatively, some patients may need to discontinue ICI.

Patients who remained on CTLA-4 or PD-(L)1 monotherapy had a 29% and 37% rate of recurrence, respectively [85••]. While this was a multicenter retrospective analysis,

this study likely under-estimated the risk of recurrence due to selection bias favoring patients with mild disease, as severe colitis and near fatal colitis would have provided unacceptable risk to restarting therapy. Indeed, one major risk factor for ICI recurrence is the use of CTLA-4 inhibitor therapy [85••]. Encouragingly, some data suggest that transitioning ICI therapy regimens may provide reduced risk of recurrence [85••, 86] as would be expected based on the distinct mechanisms of action of the drugs. One retrospective analysis reported that transitioning from CTLA-4 monotherapy to PD-(L)1 monotherapy had a 28% risk of colitis recurrence, while patients transitioning from PD-(L)1 monotherapy to CTLA-4 therapy had 88% rate of recurrence. Transitioning from combination CTLA-4 and PD-(L) blockade to anti-PD-(L)1 monotherapy may portend lower irEC recurrence risk upon restarting ICI therapy.

Given the benefit of anti-TNFα therapy in managing irEC, one case series restarted five patients on concomitant ICI therapy and infliximab after irEC resolution, without changing their ICI regimen and saw no recurrence of symptoms [85••]. Both infliximab and vedolizumab provide promising avenues for facilitating treatment re-initiation as maintenance therapies, though data supporting this approach are currently minimal.

Special Circumstances

Patients with concomitant diagnoses, including inflammatory bowel disease (IBD) and GI metastasis of malignancies, ought to be given special consideration. Due to concern for inflammatory toxicities, patients with IBD have been excluded from prospective ICI clinical trials. One prospective clinical trial (AIM-NIVO, NCT03816345) is currently enrolling patients with both ulcerative colitis and Crohn's disease for treatment with Nivolumab (anti-PD1 monoclonal antibody) [87]. This will provide much-needed information for developing risk assessment and treatment protocols.

Few retrospective studies exist to inform current treatment strategies in patients with IBD and the need for ICI therapy. One multicenter analysis included over 100 patients with IBD (both UC and Crohn's disease) on immunotherapy [20, 88••], including patients on PD-(L)1 blockade, CLTA-4, and combination therapy. Indications for treatment most commonly were melanoma or lung cancer, and patients were most often treated with PD-(L)1 blockade (85/102 patients, with 7 on CTLA-4 monotherapy and 10 on combination therapy). Here, 41% of patients developed GI irAE (21% severe, including a small number of perforations), compared to only 11% GI irAE in the control cohort. Encouragingly, no patients had fatal GI irAEs and cancer response rates were similar to published trials, suggesting that the patients benefitted from ICI therapy. Limitations of this study include selection bias for mild IBD compared to the national populations, as 50% of patients had quiescent disease off therapy (vs 25% nationally). While patients with IBD require close clinical monitoring and are at higher risk of GI irAEs, these data suggest ICI therapy may be used for responsive malignancies in this population.

Additionally, one may consider the mechanism of SIT in patients with GI malignancy [89]. Specifically, vedolizumab binds to α4β7 integrin, preventing gut-specific T cell homing. While this provides an advantageous protection against irAE, this mechanism may limit effective antitumor responses to ICI therapy in the GI mucosa. Further data is necessary to understand whether vedolizumab limits effective antitumor response.

Finally, patients with GI irAE are being treated in the context of the COVID-19 pandemic. To date, vaccination is critical in the prevention of illness. Both the American Society of Clinical Oncology and European Society of Medical Oncology have made statements supporting the use of the COVID-19 vaccine in patients on ICI therapy, so long as components of that vaccine are not contraindicated (i.e., known allergy to vaccine) [90, 91]. Current data suggest little impact on virus protection and vaccine toxicity from ICI therapy; likewise, vaccination does not impact the safety and efficacy of ICI therapy [92]. Data also suggest that patients on ICI therapy do not have an increase in cytokine release syndrome [93] or GI irAE [94], and may even have some protection against irAE, again supporting their clinical safety in patients vulnerable to irAE [93]. Finally, as per ASCO [91] and ESMO guidelines [90], patients who are immunocompromised who develop COVID-19 ought to be treated with oral antiviral therapy or monoclonal antibodies as soon as infection is confirmed [95]. We strongly believe this includes patients being treated for irAEs.

Conclusion

IrEC is the most common severe irAE leading to ICI discontinuation. Current treatment strategies reviewed herein are mostly based on expert opinion and retrospective data. More work on developing risk assessment tools and treatment protocols based on prospective clinical trials is necessary as indications for immune checkpoint therapy continue to expand.

Declarations

Conflict of Interest M Dougan has research funding from Novartis and Eli Lilly; he has received consulting fees from Tillotts Pharma, Partner Therapeutics, SQZ Biotech, AzurRx, Eli Lilly, Mallinckrodt

Pharmaceuticals, Aditum, Foghorn Therapeutics and Moderna; he is a member of the Scientific Advisory Board for Neoleukin Therapeutics. Y Badran receives consulting fees from Aditum Bio and Goodpath. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Human and Animal Rights and Informed Consent This article does not contain any studies with human nor animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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