Management of Immunotherapy Colitis: Special Considerations in the COVID-19 Era

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Conundrum: A 54-year-old woman with advanced non–small cell lung cancer who has been undergoing treatment with pembrolizumab for the past 8 weeks presents to her oncologist with a 1-week history of progressive diarrhea and fatigue. She reports 6 bowel movements per day with associated urgency and tenesmus. She denies any abdominal pain, nausea, vomiting, or fever, but endorses chills. She has no sick contacts and has not recently been treated with antibiotics. Initial evaluation with stool cultures and tests for *Clostridium difficile* infection are negative.

Immune checkpoint inhibitors (ICIs) targeting the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) and/or programmed death–ligand 1 (PD-L1) pathways have improved the prognosis for patients with a range of cancers, but they can lead to both systemic and organ-specific immune-related adverse events.[1] Of these, colitis is among the leading immune-related adverse events of checkpoint blockade.[2] The incidences of diarrhea and colitis are higher with the use of CTLA-4 blockade compared with PD-1 and/or PD-L1 blockade, with the highest incidence reported in patients who are treated with the combination of both agents.[3-5] Symptoms usually begin 6 to 8 weeks after the initiation of therapy, but can occur after the completion of treatment.[3] Diarrhea in this patient was concerning for ICI-induced enterocolitis.

The approach to the evaluation of patients with suspected ICI-induced colitis and their management is based on symptom severity. For patients with grade 3 symptoms (≥7 bowel movements per day by common terminology criteria for adverse events [CTCAE]), guidelines predating the coronavirus disease 2019 (COVID-19) pandemic traditionally have recommended immunosuppression with high-dose glucocorticoids (1-2 mg/kg).[6,7] Adjunctive biologic agents, including a tumor necrosis factor (TNF) α inhibitor (eg, infliximab) and anti-integrin antibody (eg, vedolizumab), typically are reserved for patients with steroid-refractory colitis.[6-8]

How should patients with suspected ICI toxicity be evaluated in the era of COVID-19? Are adjustments in the current evaluation algorithm needed in light of the potential risk of infection?

COVID-19, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly emerged as a global pandemic. Patients with COVID-19 most commonly present with fever, dry cough, myalgia, or fatigue, but the disease can rapidly progress to cause acute respiratory distress syndrome and death. Gastrointestinal symptoms also have been reported in patients with COVID-19 and can be the initial presenting symptom.[9] Diarrhea in patients with COVID-19 does not appear to be severe.[9,10] However, given the increasing community spread of COVID-19 and the overlap between symptoms of ICI colitis and COVID-19 infection, patients should be screened carefully for other COVID-19–related symptoms and exposures. Testing should be considered to exclude infection and is usually performed using polymerase chain reaction for SARS-CoV-2 on a respiratory tract specimen. Stool calprotectin can also be particularly helpful in this situation because an elevated level may be indicative of intestinal inflammation from ICI colitis, but it does not obviate the need for SARS-CoV-2 testing and has limitations with regard to its sensitivity (eg, ICI enteritis).[6] The presence of colitis on abdominal computed tomography (CT) scan can support the diagnosis of ICI colitis and rule out complications.

Testing for COVID-19 using polymerase chain reaction on a nasopharyngeal swab is found to be negative, fecal calprotectin is found to be elevated at 450 μg/g, and an abdominal CT scan has demonstrated diffuse wall thickening in a fluid-filled colon with mucosal hyperemia. What are the risks of using steroids for ICI colitis within the setting of the COVID-19 pandemic, and are adjustments to the present evaluation and/or treatment algorithm needed?

Elevated fecal calprotectin, negative stool cultures, and the presence of colitis on abdominal CT scan support the diagnosis of ICI colitis. However, they are not specific for ICI colitis.[11] Prior guidelines have suggested that treatment with corticosteroids be initiated for patients with suspected ICI colitis and that endoscopic evaluation can be performed within 2 weeks among these individuals.[6] During the COVID-19 pandemic, we suggest endoscopic evaluation be performed earlier to confirm the diagnosis, rule out other causes of colitis (eg, cytomegalovirus infection), and promptly direct therapy. This approach is based on the theoretical risk that supraphysiologic doses of glucocorticoids and other immunosuppressive agents may increase the risk of SARS-CoV-2 acquisition through diminished control of viral replication.

Both upper endoscopy and colonoscopy are considered to be aerosol-generating procedures. Because COVID-19 can be asymptomatic, testing for SARS-CoV-2 generally should be performed prior to these procedures.[12] Proper personal protective equipment and infection control practices are also essential to preventing the transmission of COVID-19.[12]

In the setting of the COVID-19 pandemic, for patients with new grade 2 symptoms of ICI colitis, rather than initiating treatment with systemic prednisone, an initial trial of glucocorticoids with low systemic bioavailability such as budesonide may be considered. Although budesonide has not been proven effective for the prevention of enterocolitis from treatment with ipilimumab, limited data have suggested that it can control symptoms and prolong the duration of immunotherapy.[13,14]

Corticosteroid enemas can also alleviate symptoms of urgency and tenesmus in patients with rectosigmoid inflammation. In patients who fail to improve and those with grade 3 colitis, transition to biologic agents (eg, TNF-α inhibitor infliximab or anti-integrin vedolizumab) rather than an initial trial of high-dose glucocorticoids (prednisone at a dose of 1-2 mg/kg) may be considered. This approach is supported by data from an observational, registry-based study that included 525 patients with inflammatory bowel disease (IBD) with confirmed COVID-19 in whom the use of corticosteroids, but not anti–TNF-α therapy, was associated with an increased risk of severe COVID-19.[15] Rates of severe COVID-19 in patients receiving anti-integrin therapy appeared to be low. Although causality cannot be established, it is biologically plausible that steroids may increase the risk of infection due to their immunosuppressive effect.

In another retrospective cohort study that included 37,857 patients with IBD, 1759 of whom were receiving anti–TNF-α therapy, 1 patient developed COVID-19 (incidence of 0.57 per 1000 patients). In adjusted analyses, increasing comorbidity scores but not anti–TNF-α therapy were associated with an increase in the risk of COVID-19.[16] Retesting for COVID-19 prior to the initiation of treatment may be prudent if not performed within the last 48 hours.[17]

In patients who are treated with glucocorticoids and demonstrate a response, in the absence of a COVID-19 infection, we suggest that glucocorticoids not be discontinued abruptly. Abrupt discontinuation can cause a flare of the underlying colitis. Prednisone should be tapered over 3 weeks or as tolerated. For patients who are treated with vedolizumab or infliximab who respond but require additional doses for the resolution of colitis, limited data have suggested that these can be continued safely.[15]

Management of Patients With COVID-19 and ICI Colitis

The management of patients with both COVID-19 infection and ICI colitis must be individualized based on both the severity of COVID-19 and the risk of ICI-related gastrointestinal complications, which in severe cases can include perforation. These patients require close monitoring of their disease trajectory. Although budesonide and topical steroids are likely safe to use due to their low systemic bioavailability and gastrointestinal consensus guidelines in patients with IBD have recommended continuing these agents in patients with COVID-19, to our knowledge data concerning their safety in patients with COVID-19 are lacking.[18] Biologic agents ideally are avoided in patients with COVID-19 due to their long half-life. A role for the blockade of TNF-α in the treatment of the COVID-19 inflammatory cascade has been suggested in a case report, but additional data are needed.[19] The role of systemic glucocorticoids in the treatment of COVID-19 is rapidly evolving. Systemic glucocorticoids are used in patients with early acute respiratory distress syndrome and/or marked inflammatory responses to COVID-19.[20] Emerging data from a large, randomized, open-label trial have suggested a role for dexamethasone in patients with severe COVID-19 who require oxygen or ventilatory support, with a reduction in 28-day mortality noted among hospitalized patients compared with usual care alone.[21] In contrast, no benefit was noted among patients who did not require oxygen and/or ventilatory support, and there was a nonstatistically significant trend toward a higher mortality. Similarly, interleukin 6 pathway inhibitors (eg, tocilizumab, sarilumab, and siltuximab) are being evaluated in patients with severe COVID-19 and cytokine release syndrome. Interleukin 6 receptor blockade has been associated with gastrointestinal perforation, but cases appear to have occurred largely among patients with diverticulitis and those receiving nonsteroidal anti-inflammatory drugs and/or long-term glucocorticoids. To our knowledge, tocilizumab has not been evaluated in patients with ICI colitis, but it has demonstrated some benefit in patients with active Crohn disease.[22] If tocilizumab is used to treat severe COVID-19 pneumonia, it should be done with extreme caution in patients with coexisting ICI colitis, and these patients should be monitored closely for early signs of perforation.

The management of patients with cancer with suspected ICI colitis has been particularly challenging during the COVID-19

pandemic. Mitigating the risk of infection has required modifications in both the current diagnostic and treatment algorithms. To our knowledge, data with which to guide the management of patients with both ICI colitis and a COVID-19 infection are lacking, and treatment decisions must be individualized.

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Shilpa Grover is employed as a deputy editor for gastroenterology at UpToDate, Wolters Kluwer Inc. Sheila Bond is employed as a deputy editor for infectious diseases at UpToDate, Wolters Kluwer Inc. Michael K. Mansour has acted as a paid consultant for Vericel Corporation, SmartPharm Therapeutics, Pulsethera Corporation, GenMark Diagnostics, and Globe Life Sciences; has received grant support from Thermo Fisher Scientific; has received personal fees for medical writing and/or editing from UpToDate; has acted as a paid member of the scientific advisory board for Celularity; and has received personal fees for editing from the Infectious Diseases Society of America. In addition, Dr. Mansour has a patent Cellular Therapeutics for Treatment of Neutropenic Patients (US no. 15/999,463) pending. Sonia Friedman made no disclosures.

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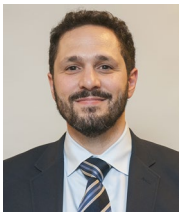

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