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ORIGINAL ARTICLE

Calcineurin inhibitors in steroid and anti-TNF-alpha refractory immune checkpoint inhibitor colitis

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calcineurin inhibitor, checkpoint inhibitor colitis, immunotherapy.

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Abstract

Background and Aim: Immune checkpoint inhibitor (ICI) colitis is an increasingly common problem encountered as the use of checkpoint inhibitors (CPIs) grows in the management of cancers. Corticosteroids and tumour necrosis factor (TNF)-alpha inhibitors are widely recommended in the management of ICI colitis; however, the experience is limited when patients are refractory. Different authors have reported success with vedolizumab, mycophenolate, and cyclosporine. This case series describes our experience with calcineurin inhibitors in the management of corticosteroid and anti-TNF-alpha refractory ICI colitis.

Methods: Data from electronic medical records were identified and reviewed retrospectively from a cohort of patients treated at a single oncology center. All patients who were identified between March 2018 and May 2020 with ICI colitis refractory to treatment with infliximab and corticosteroids were included.

Results: There were 11 patients who developed ICI colitis after receiving CPIs for advanced melanoma and required rescue therapy with either cyclosporine or tacrolimus after treatment failure of infliximab. Median age was 53 (±8.48) years, with nine patients (81%) receiving combination Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) / programmed cell death protein 1 (PD-1) immunotherapy. Median time after first CPI infusion to ICI colitis was 4.43 (±19.53) weeks. The median time from onset of symptoms to commencement of rescue therapy with calcineurin inhibitors was 70 days (±66.06). Eight of the 11 patients (72.7%) responded to calcineurin inhibition. In patients who responded, calcineurin inhibitors were continued for a median of 54 (±28.96) days.

Conclusion: The calcineurin inhibitors cyclosporine and tacrolimus appear to be a safe and effective option for the management of patients with infliximab-refractory ICI colitis. The therapeutic benefit is observed rapidly, and adverse effects appear to be limited with close monitoring.

Introduction

Checkpoint inhibitors (CPIs) are playing an increasing role and changing the landscape in the management of a variety of malignancies, including melanoma, non-small cell lung cancer, head and neck cancers, and renal cell cancer.[1] While these therapies have had a dramatic impact on cancer survival, these benefits are accompanied by immune-related adverse effects (irAEs), which may cause significant morbidity and may also disrupt further cancer therapy. Accordingly, clinicians are increasingly confronted with irAE, which may represent a difficult and, at times, nuanced management problem.

The gastrointestinal tract is frequently affected by irAE, with immune checkpoint inhibitor (ICI) colitis being a common problem encountered. This is likely due to high numbers of regulatory T-cells (T_{reg}) residing in the intestinal mucosa, which express CTLA-4 and are important in maintaining immune tolerance. ICI colitis occurs in up to 40% of patients who receive CPIs.[1] The choice of agent appears to be an important factor, with CTLA-4 inhibition more commonly implicated compared to PD-1 and PD-L1 inhibition. Time of onset usually occurs within 10 weeks after the second or third CPI infusion,[2] although ICI colitis may occur years after commencing therapy in some patients.

ICI colitis usually presents with nonbloody diarrhea, and its severity can be graded according to the Common Terminology Criteria for Adverse Events.[3] Oral corticosteroids are widely recommended as first-line treatment in those with colitis of grade 2 or higher, and further immunotherapy should be withheld until resolution of symptoms and corticosteroid therapy has been tapered. For severe colitis (grade 3 or 4), high-dose oral corticosteroids or intravenous corticosteroids are recommended, with a gradual wean as symptoms improve. Infectious causes should be

excluded with stool examination [microscopy, culture ± polymerase chain reaction (PCR) testing]. Endoscopic assessment with mucosal biopsies is important to confirm the diagnosis and exclude alternative causes. Although there is poor correlation between the grade of colitis and endoscopic Mayo score,[4] a higher score and the presence of ulcers appear to predict the need for further immunosuppression.[5] Approximately 30% of patients with ICI colitis do not respond to corticosteroids alone. There is evidence to support the use of infliximab, a monoclonal antibody that neutralizes circulating and membrane-bound TNF-alpha molecules, in this subset of patients.[6] For patients who fail to respond or relapse soon after treatment with anti-TNF therapy, the data surrounding the choice of immunosuppressive agent is lacking. Current practice is guided by case reports and small case series.[7–9] Different authors have reported success with vedolizumab, mycophenolate, and cyclosporine.

Vedolizumab is a monoclonal antibody that binds to α4β7 receptors present on circulating lymphocytes, which inhibits adhesion to endothelial receptors (MAdCAM-1) in gut blood vessels. This allows for a gut-specific mechanism of action, preventing T-cell migration into the intestinal mucosa.[2] The efficacy of vedolizumab in achieving clinical remission in patients with ICI colitis was demonstrated in a case series of seven patients in 2017.[7] However, only one patient in this series had received infliximab prior to the vedolizumab infusion. In a multicenter trial of 28 patients, only 9 patients received vedolizumab after infliximab, with 6 of these 9 patients achieving clinical response.[8]

The calcineurin inhibitors tacrolimus and cyclosporine inhibit T-cell activation by inhibiting interleukin-2 (IL-2) release. IL-2 has important roles in promoting immune tolerance and reducing autoimmune inflammation. There is one case report of successful cyclosporine use in a patient with metastatic non-small cell cancer with ICI enterocolitis[10] after nonresponse to steroids and infliximab.

Mycophenelate mofetil (MMF), which exerts immunosuppressive effects by inhibiting T- and B-cell replication through Inosine-5′-monophosphate dehydrogenase (IMPDH) inhibition, has been used in conjunction with corticosteroids for patients with ICI colitis. In a single-center prospective study, 11 patients with ICI colitis were treated with combination MMF and corticosteroids upfront. Seven patients responded well. Four of 11 patients subsequently required infliximab rescue therapy despite MMF and corticosteroids but quickly went into clinical remission.[9] MMF has also been used successfully in a single case refractory to both infliximab and vedolizumab.[11]

We present a case series of patients who were treated in our institution for ICI colitis refractory to corticosteroids and infliximab and who were then treated with calcineurin inhibitors (cyclosporine or tacrolimus).

Methods

Data from electronic medical records were identified and reviewed retrospectively from a cohort of patients treated at a single oncology center. All patients who were identified between March 2018 and May 2020 with ICI colitis refractory to treatment with infliximab and corticosteroids were included. Treatment failure was defined as persistent or recurrent gastrointestinal symptoms that were grade 2 or higher at least 7 days after receiving infliximab. Clinical, endoscopic, and histologic data were extracted from the electronic records and specialist outpatient letters.

Results

Patient characteristics. There were 11 patients identified (Table S1, Supporting information) who developed ICI colitis after receiving CPIs for advanced melanoma and required rescue therapy with either cyclosporine or tacrolimus after treatment failure of infliximab (Table 1). Median age was 53 (±8.48) years. Nine patients (81%) had Stage IV disease. Nine patients (81%) had received combination CTLA-4 and PD-L1 immunotherapy. Two patients received PD-L1 inhibitor monotherapy. One of these patients developed mild symptoms that responded to oral steroids. This patient was subsequently retreated 664 days after her first infusion with two cycles of combination CPI therapy for relapsed melanoma and experienced a relapse of colitis, which required infliximab after failing to respond to oral steroids. One patient who received combination CTLA-4/PD-1 therapy had a history of ulcerative colitis (UC), which had been in long-standing remission on sulfasalazine and azathioprine prior to the diagnosis of metastatic melanoma.

Stool examination. Four patients (36.3%) had a positive stool examination. *Campylobacter jejuni*, *Blastocystis hominis*, *Aeromonas caviae*, and adenovirus were identified and treated on discussion with infectious diseases colleagues. Treatment did not

Table 1 Patient characteristics (n = 11)

Patients	Number of patients (%)
Mean age (SD)	68 (±13.65)
Male	7 (63.6)
Cancer type: melanoma	11 (100)
Cancer stage	
Stage III	2 (18.2)
Stage IV	9 (81.8)
Checkpoint inhibitor subtype	
CTLA-4 monotherapy	0 (0)
PD-L1 monotherapy	2 (18.2)
Combination therapy	9 (81.8)
Other organ toxicities	
Thyroiditis	1 (9.1)
Hepatitis	1 (9.1)
Pancreatitis	2 (18.2)
Hypophysitis	2 (18.2)
Neuropathy	1 (9.1)
Grade of colitis	
I	0
II	1 (9.1)
III	9 (81.8)
IV	1 (9.1)
Bloody diarrhea	3 (27.2)
Alive	8 (72.7)

SD, standard deviation.

alter symptoms or outcomes in all four patients, which suggests that these were incidental rather than pathogenic.

Fecal calprotectin. Eight of 11 patients had a fecal calprotectin collected. The mean recorded fecal calprotectin was 938 (±1077.79) μg/g.

Endoscopic features. All but one patient underwent two or more endoscopic procedures. At the first endoscopic examination, eight patients (72.7%) had features of inflammation, with loss of vascular pattern, mucosal edema, and erythema (Table S2). Two patients had ulcers on first endoscopic inspection. Two patients had normal mucosa found at endoscopy but microscopic changes identified on histology, and one patient had normal endoscopy and biopsies (Figs 1,2).

Histologic features. Histological examination most commonly demonstrated both chronic and acute colitis (Table S3). The colonic mucosa appeared normal in two patients; however, one of these patients had features of lymphocytic colitis on histology despite normal endoscopy.

Time to therapy. Median time after first CPI infusion to symptoms of ICI colitis was 4.43 (±19.53) weeks, with symptom onset generally occurring after the second cycle (Table 2). The median time from onset of symptoms to first infliximab infusion was 22 (±55.07) days. The median time from the onset of symptoms to commencement of rescue therapy with calcineurin inhibitors was 70 days (±66.06).

Eight of the 11 patients (72.7%) responded to calcineurin inhibition. In patients who responded, calcineurin inhibitors were continued for a median of 54 (±28.96) days.

Assessment of response to cyclosporine was not possible in two patients who died from bowel obstruction due to progression of metastatic disease (days 7 and 23 following administration of cyclosporine). One patient had recurrent renal impairment attributed to cyclosporine. This patient was not considered a surgical candidate due to involvement of the small bowel and was treated with three doses of vedolizumab without a clinical response. This patient required total parenteral nutrition due to protein-losing enteropathy and subsequently responded to treatment with enteric-release budesonide and mycophenolate.

Outcomes from malignancy and need for ongoing therapy. Three of 11 patients died within 12 months of developing ICI colitis, all from complications arising from the progression of intra-abdominal metastatic melanoma. Five patients remained stable and did not require further CPI. Three patients received further CPI with PD-L1 inhibition for progressive melanomatous disease. Of this group of patients, one patient received a second course of cyclosporine for suspected recurrent ICI colitis and responded.

Side effects. Calcineurin inhibition was generally well tolerated. Prior to treatment, all patients were screened for hepatitis B and C viruses, varicella zoster, Epstein Barr Virus, cytomegalovirus, and fasting lipids. All patients received *Pneumocystis jiroveci* prophylaxis with trimethoprim/sulfamethoxazole. One patient developed renal impairment due to ciclosporin toxicity and was transitioned to tacrolimus. This patient also developed acute kidney injury with tacrolimus.

Discussion

This series demonstrates that calcineurin inhibitors are safe and effective in a cohort of patients with moderate to severe

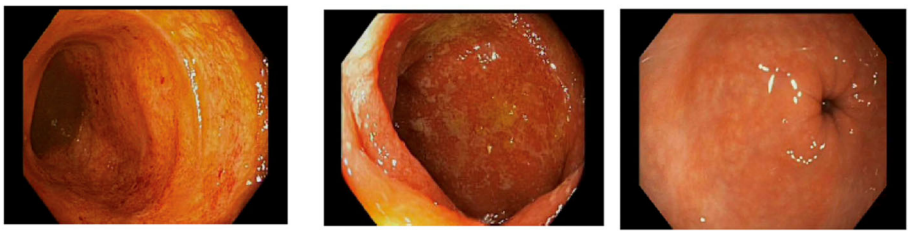

Figure 1 Inflammatory features at endoscopy.

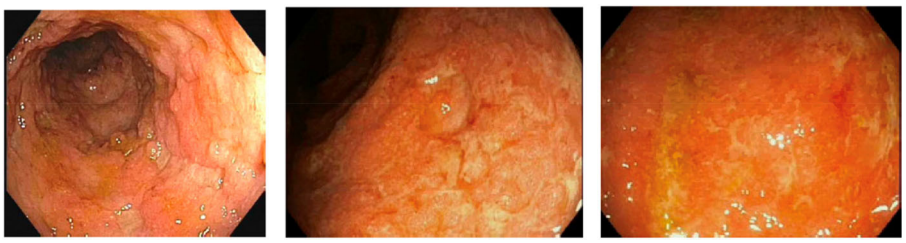

Figure 2 Ulceration.

Table 2 Time to therapy

Parameters	Number
Median time to colitis in weeks (SD)	4.43 (±19.53)
Median number of checkpoint inhibitor infusions to colitis (SD)	2 (±2.07)
Median time from symptom onset to infliximab in days (SD)	22(±55.07)
Median time from first infliximab infusion to calcineurin inhibitor or third-line therapy in days (SD)	33 (±28.01)
Median time from colitis to calcineurin inhibitor or third-line therapy in days (SD)	70 (±66.06)
Bactrim prophylaxis (%)	11 (100%)
Median duration of follow up in days (range)	126 (±161.23)
Response of colitis with calcineurin inhibitor	9 (81.8%)
Duration of calcineurin inhibitor in those who achieved remission in days (SD)	54 (±28.96)

SD, standard deviation.

corticosteroid- and infliximab-refractory ICI colitis. Cyclosporine and tacrolimus exert potent immunosuppression by inhibiting calcineurin within T-cells. Calcineurin activates IL-2 and the immune response.[12] IL-2 is central to maintaining self-tolerance by supporting T regulatory cell function. Accordingly, suppression of IL-2 can predispose to autoimmunity.[13] Oral cyclosporine doses at this center were initiated at 5 mg/kg in a split twice-daily dosing. It is our practice to measure a trough level 48 h after the first dose. Doses are adjusted to achieve trough levels of 100–200 ng/mL (cyclosporine) or 8–12 ng/mL (tacrolimus). Patients thought to have impaired absorption are given intravenous cyclosporine (2 mg/kg over 24 h) and are transitioned to oral ciclosporin after 48 h if a significant response has been achieved (resolution of symptoms).

We found adverse events associated with calcineurin inhibitors to be rare; however, we monitored patients closely for hypertension, renal impairment, and neurotoxicity. Fasting serum triglycerides were routinely measured prior to commencement to identify those at higher risk of neurological adverse effects.

The utility of administering further infliximab after nonresponse to two doses of infliximab is low[14]; hence, the impetus to look for an alternative agent. There are several reasons why calcineurin inhibitors have been preferred in our institution compared to other agents such as vedolizumab. First, a quicker onset of action is desirable in patients with severe and prolonged symptoms. In comparison, vedolizumab's peak effect is seen at weeks 10–14.[15] This was certainly a factor in one of our patients whose resection of a metastatic lesion was delayed by his prolonged enterocolitis. In the largest study to date, a median of three vedolizumab infusions were required to achieve a satisfactory response for those who had failed infliximab.[8] Second, vedolizumab was less effective in those who had failed infliximab compared to those who were infliximab naïve, with response rates of 67% and 95%, respectively. Although a small cohort, 81% of our patients who had all failed infliximab responded to calcineurin inhibitors. This suggests that calcineurin inhibitors are more likely to be effective, and faster at that, in this refractory group. This is an important consideration in patients with ICI colitis, particularly those who are elderly and frail. Third, calcineurin inhibitors are far less costly compared to biologic agents. Fourth, vedolizumab has the potential to create an immune sanctuary site in the gastrointestinal tract, which may infer an increased risk of gastrointestinal metastases; however, this has not been assessed in analyses thus far. However, the targeted mechanism of vedolizumab may render it less likely to counter the therapeutic effects of CPI on melanoma.[16]

Although ICI colitis and acute severe ulcerative colitis (ASUC) share similar clinical features and management, it is important to bear in mind that they are different entities, each with a distinct underlying disease process, and that the approach needs to be tailored accordingly. UC and ICI colitis may be clinically, endoscopically, and histologically indistinguishable in those with preexisting disease. However, the characteristics of each are very different. In comparison to patients with inflammatory bowel disease (IBD), patients with ICI colitis are older, have more comorbidities, and have been usually exposed to a more prolonged course of corticosteroid. In our cohort, all patients were on a dose of corticosteroids greater than 10 mg for over 10 weeks. The use of successive immunosuppression in ASUC is not advised as the risk of adverse events, primarily bacterial sepsis, is as high as 16–23%.[17–19] Colectomy is thus recommended after failure of salvage therapy with TNF-alpha or calcineurin inhibitor in ASUC. This is where another key difference lies. The overall disease course is shorter in ICI colitis as it relates to a specific insult, which is identifiable and modifiable (CPIs). This is in contrast to IBD patients who need prolonged, if not lifelong, immunosuppression. Furthermore, ICI colitis, unlike ASUC, is a dynamic process where enteritis can develop with time. Not only do the differences in patient characteristics render the risks of surgery higher in ICI colitis compared to ASUC, they are also not definitively curative. This was the case in one of our patients who developed ICI enteritis after subtotal colectomy for infliximab refractory colitis. He received cyclosporine 14 days postoperatively with response. This serves to highlight that the risks of surgery outweigh that of successive immunosuppression in ICI colitis.

The management of ICI colitis in patients with IBD is another challenging issue to navigate. We had one patient who had a diagnosis of quiescent UC preceding that of metastatic melanoma. Prior to commencement of CPI, the patient was counseled on the high risk of UC flare. The risks of prophylactic, pre-CPI biologics was not thought to be justified. TNF-alpha would not be ideal in the setting of metastatic melanoma, and vedolizumab would theoretically reduce the threshold of melanomatous spread to the gastrointestinal tract. The patient developed colitis after the second CPI infusion, for which he received corticosteroids and infliximab. He remained steroid dependent 2 months later despite three further doses of infliximab (at another institution). The risk of sepsis-related complications with sequential infliximab followed by cyclosporine were carefully weighed against the risks of colectomy. The decision surrounding successive cyclosporine and infliximab is a difficult one in IBD patients with ICI colitis. We elected to proceed with salvage ciclosporin therapy partly informed by the expectation that the effect CPI therapy had on the preexisting colitis would wane with time and that the colitis may therefore return to its preexisting, indolent behavior. The concern for progressive ICI enteritis despite surgery, as discussed earlier, also factored into

the decision. The patient experienced a swift and gratifying clinical response to cyclosporine.

Two patients died of complications from metastatic melanoma, at 1 and 3 months after first infliximab infusion. The role of TNF-alpha inhibition in accelerating carcinogenesis has been an ongoing concern. This is reflected in the black box warnings required by the United States Food and Drug Administration.[20] However it is unlikely that TNF-alpha inhibition played a clinically significant role in accelerating carcinogenesis in these two patients as they had extensive melanomatous disease at commencement of immunosuppression. Furthermore, there is no evidence in other series of an increased risk of recurrent melanoma in patients treated with anti-TNF agents. On the contrary, the balance of evidence suggests that ICI colitis may predict favorable survival outcomes presumably as a reflection of a more robust immune response to both tumor and colonic self-antigens. This is based on an analysis which demonstrated that ICI colitis overall survival was significantly better compared to those without diarrhea.[1]

Our case series demonstrates that calcineurin inhibitors are viable options for patients with ICI colitis refractory to anti-TNF therapy. Although there have been no head-to-head studies performed with vedolizumab, the rapid onset of action of calcineurin inhibitors suggests that this class of medication is favorable in unwell patients with severe colitis who require rapid, steroid-sparing treatment. The favorable long-term side effect profile of vedolizumab may render its use more appealing in frailer patients at risk of calcineurin inhibitor toxicity or those who may require extended therapy. Vedolizumab may also have a role as an additional therapy in patients such as ours in this series, with ongoing colitis despite steroids, infliximab, and calcineurin inhibitors.

Conclusion

The calcineurin inhibitors cyclosporine and tacrolimus appear to be a safe and effective option for the management of patients with infliximab-refractory ICI colitis. The therapeutic benefit is observed rapidly, and adverse effects appear to be small on close monitoring.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Patient characteristics.
Table S2. Features at first endoscopy.
Table S3. Histological characteristics at first endoscopy.