Review Article

Treatment of immune checkpoint inhibitor-related colitis: a narrative review

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Background and Objective: Cancer is one of the most difficult diseases facing modern medicine, and increasing amounts of research and clinical treatments are being applied to the treatment of cancer. Immunotherapy, particularly immune checkpoint inhibitor (ICI) therapy, has revolutionized the treatment and overall survival of patients with several different types of cancer. Approximately one-third of patients treated with ICIs may experience immune-related adverse events (irAEs). Immune checkpoint inhibitor-associated colitis (ICIC) is the most common irAE with an incidence of approximately 8–10%, ICIC usually presents as watery or bloody diarrhea, and if the symptoms are severe, ICI treatment must be interrupted or even terminated. This review summarizes the epidemiology, pathogenesis, clinical characteristics, and therapies of ICIC, focusing on the use of biologics, in order to propose treatment options in different situations to control immune checkpoint inhibitor-related colitis as soon as possible.

Methods: To find relevant articles for this narrative review paper, a combination of keywords such as immune checkpoint inhibitor-related colitis, corticosteroids, biologics were searched for in PubMed databases.

Key Content and Findings: The pathogenesis of ICIC is complex and primarily involves antitumor effects and indirect damage to colonic tissues, as well as the activation of specific proinflammatory pathways. Corticosteroids (CSs) are the first line of treatment for ICIC, but steroid-refractory or steroid-resistant cases often occur. Patients with irAE colitis respond favorably to biologics, and patients with CS-resistant/refractory enterocolitis can benefit from the early use of biologics.

Conclusions: Biologics are currently recommended for the treatment of ICIC but are usually used as a supplement after the failure of first-line CS therapy. Patients with irAE colitis respond favorably to biologics, and patients with CS-resistant/refractory enterocolitis can benefit from the early use of biologics. Biologics (alone or in combination with CS) should be considered as an early therapy option for high-risk patients rather than just an escalation after a failure to respond to CS.

Keywords: Immune checkpoint inhibitor-associated colitis (ICIC); corticosteroid (CS); biologics; infliximab (IFX); vedolizumab (VDZ)

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Introduction

Immunotherapy refers to a broad range of methods for treating cancer that generate or boost the immune response to cancer, and represents a breakthrough in cancer treatment. Immune checkpoint inhibitors (ICIs) are a type of immunotherapy that consist of monoclonal antibodies that attempt to strengthen and revitalize the immune system by binding to coinhibitory receptors, prompting immune-mediated tumoral cell death (1). Because of their advantages in terms of therapeutic efficacy, including an unprecedented and durable antitumor response rate, ICIs have completely changed the therapeutic landscape for patients with a variety of cancer types. Currently, approved ICIs are directed against cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed cell death ligand 1 (PD-L1). PD-1 and PD-L1 are coinhibitory proteins expressed by lymphocytes and antigen-presenting cells (APCs) that induce self-tolerance and autoimmunity regulation, while CTLA-4 is expressed in T cells and B cells and negatively regulate lymphocyte activation (2).

ICIs have shown excellent antitumor activity in a variety of cancers; however, ICIs can cause multiple organ damage and unique side effects called immune-related adverse events (irAEs). These irAEs affect virtually every organ system and can lead to significant morbidity, mortality and impaired quality of life. The systemic augmentation of immune responses by ICIs, especially when they are used in combination, can lead to a range of immune-related toxicities (3). Fortunately, these immune-mediated toxicities are largely reversible (4), but they require early, precise identification and timely intervention. One of the most common adverse events (AEs) is colitis, which can significantly lower a patient's quality of life, and force antitumor medication to be stopped or halted. In clinical practice, the first-line treatment for irAE colitis is corticosteroids (CSs) (5). Further, biologics such as infliximab (IFX) and vedolizumab (VDZ) have gradually attracted attention, but they are often used as complementary treatments or as an upgrade after failure of the first-line treatment for irAE colitis.

The mechanism and effectiveness of first-line steroid therapy, and second-line biologics and other treatments for irAE colitis have not yet been fully summarized, and the pathogenesis and pathophysiology of irAE colitis remain unclear. Therefore, at present, there is no consensus as to when biologics should be used and which biologics should be administered. This review summarized the current mechanisms behind irAE colitis and its evidence-based management with an emphasis on the role of biological therapies to elucidate the mechanism, effectiveness, and safety of therapies for treating irAE colitis. Mechanism-based approaches will enable the application of appropriate treatment options for patients with irAE colitis, especially those with refractory irAE colitis. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-2150/rc).

Methods

A literature search was conducted of the PubMed database using the following keywords: "Immune checkpoint inhibitor-related colitis" AND "Corticosteroids" AND "Biologics" (*Table 1*). Only research articles written in English were considered, and no predefined restrictions were set in terms of the study type. The data sources were independently screened by two authors. The data analysis was conducted by two authors.

Epidemiology

The lower gastrointestinal (GI) tract is the most commonly affected by ICI-related GI AEs. Colitis is defined as the presence of mucosal inflammation. It has been reported that the incidence of irAE colitis is 0.7–1.6% with anti-PD-1 therapy, 5.7–9.1% with anti-CTLA-4 therapy, and nearly 13.6% with the combination of anti-PD-1/PD-L1 and anti-CTLA-4 therapies (6-8). Overall, compared to anti-PD-1/PD-L1 therapy, anti-CTLA-4 therapy is more likely to result in immunological-related diarrhea and colitis. To date, there is no evidence that sex, tumor type, and the severity of immune-mediated colitis are significantly correlated (9). Colitis can develop any time after starting ICI medication, but occurs earlier with PD-1 inhibitors, and has a greater severity with anti-CTLA-4 therapy, and combination therapy in particular (9-12).

Mechanism

The exact mechanism of immune checkpoint inhibitor-associated colitis (ICIC) has not been defined; however, the current research results support the hypothesis that the proinflammatory response plays an important role in this process, causing a proinflammatory status and the

Table 1 Summary of search strategy

Items	Specification
Dates of searches	01 June 2024 to 01 August 2024
Database	PubMed
Search terms	"Immune checkpoint inhibitor-related colitis" AND "Corticosteroids" AND "Biologics"
Timeframe	1995–2024
Inclusion and exclusion criteria	Inclusion criteria: all study types
	Exclusion criteria: articles published in languages other than English
Selection process	S.W. and H.W. independently screened the data sources. The data analysis was conducted by S.W. and H.W.

emergence of an autoimmune-type presentation (13-15). According to Luoma *et al.*, the overactivation of tissue-resident cluster of differentiation (CD)8^+ T cells is a significant factor in colitis (16). Additional $CD8^+$ and $CD4^+$ T-cell populations are subsequently drawn from the blood on the activation of these T cells. Because a healthy colon already has a significant number of these tissue-resident $CD8^+$ T cells, irAE colitis develops relatively early following the administration of ICIs. The development of ICIC is significantly influenced by the abundance of CD8 tissue-resident T cells in the colon, and their activation promotes the assembly of CD4 and CD8 T cells accompanied by the release of granzymes. CD8 tissue-resident memory T cells have been shown to be the dominant immune cell population in ICIC, and those located near the epithelial border drive its cytotoxicity (17). The blocking of immune checkpoints can achieve significant tumor regression in some patients; however, the systemic activation of autoreactive T cells damages off-target host tissues, causing a range of toxicities (4). Several animal models lacking immune checkpoints have been used to simulate the immunological effects of checkpoint inhibitor-associated colitis. Mice with the CTLA-4 deletion exhibit broad immune cell infiltration in numerous organs and lethal colitis due to enhanced T-cell activity (18-20).

Additionally, cytokines may play a part in ICIC. A preclinical model of ICIC has been shown to increase interleukin-17 (IL-17) (21,22), while inducible genes and the expression of interferon-γ (INF-γ) and tumor necrosis factor-α (TNF-α), which induce cell death, are substantially increased in ICIC patients (16,23). The expression of tumor necrosis factor-like cytokine 1A (TL1A) and its receptor death receptor 3 (DR3) is also upregulated in ICIC (24). In addition, the recombinant chemokine C-X-C-motif receptor 3 (CXCR3) and CXCR6 chemokine receptor (CXCR9/10 and CXCR16) genes are highly expressed in colitis-related T-cell populations, and increase T-cell activity (25). The development of irAE colitis may also be facilitated by the production of cytokines from cytotoxic T lymphocytes (CTLs) and the increased expression of chemokine receptor genes in colitis-associated T cells.

ICIs regulate microbiota-gut barrier homeostasis by causing apoptosis in intestinal epithelial cells, which disrupts barrier function. Pathogenic helper T 17 cells can further lead to an imbalance in the homeostasis of the gut microbiota resulting in severe intestinal toxicity, similar to the early signs of colitis (12). A negative link between anaerobic antibiotic treatment and the severity and prognosis of colitis has been shown recently, mirroring the importance of the gut microbiota and ecological dysbiosis in the pathogenesis of ICIC.

Clinical characteristics

ICIC has a variety of clinical symptoms. The most common symptom is diarrhea, and other symptoms include fever, abdominal discomfort, distention, mucus, blood in the stool, and peritoneal symptoms. Based on our clinical practice, as a symptom of ICIC, diarrhea is characterized by its frequent occurrence at night, and thus differs from diarrhea caused by other GI diseases. In most cases, ICIC appears quickly after the start of therapy, but it may also present later in the course of treatment (26-29). The diagnostic elements of ICIC include obtaining a complete and detailed history, ruling out the cause of infection, and assessing the degree of inflammation. Since many anticancer treatments also have GI side effects, it is critical to obtain a complete drug history in actual clinical studies and treatments. Because

of the poor immune function of cancer patients, infection must be ruled out before diagnosis. The most common screening methods for infections are *Clostridium difficile* and cytomegalovirus tests. Colonoscopy is the gold standard for diagnosing ICIC, and is advised for patients with grade 2 or higher diarrhea. Endoscopic observations may vary from a nearly normal appearing mucosa to alterations such as mucosal erythema, loss of vascular pattern, edema, ulcerations, friability, and necrosis (30,31). Endoscopic and histological findings can sometimes differ, and normal mucosa can be found in roughly one-third of patients with ICIC (9). Thus, even if no clear evidence of inflammatory injury is observed endoscopically, biopsies of normal mucosa are necessary.

Biopsies are frequently used to aid in diagnosis; however, histopathological results are nonspecific (32). The main histological manifestations are neutrophilic infiltration, cryptitis, crypt abscesses, and chronic apoptosis changes such as intraepithelial lymphocytosis, crypt distortion, Paneth cell metaplasia, or basal plasmacytosis (33-35), which can also be seen in inflammatory bowel disease (IBD). Radiographic imaging is not required for the diagnosis of ICIC, but it can provide useful information, especially when there are no characteristic findings in the endoscopic evaluation. In some patients, computed tomography scans show bowel wall thickening, mesenteric vascular engorgement, fat stranding, and fluid-filled bowel (36).

When ICIC symptoms appear, their severity can be determined systematically using the Common Terminology Criteria for Adverse Events (CTCAE) (37): grade 1 irAE colitis causes asymptomatic or mild diarrhea; grade 2 colitis presents as mild abdominal pain, diarrhea, and hematochezia; grade 3 and grade 4 colitis are characterized by severe abdominal pain and frequent diarrhea, which can result in bleeding, intestinal obstruction, peritonitis, necrosis, and intestinal perforation; while Grade 5 colitis can be fatal (30,33,38,39). Diffuse enteritis occurs alone or in association with colitis in 25% of patients (40). While rare (0.3–1.3%), fatal AEs associated with ICIs primarily include colitis and toxic megacolon with colonic perforation, which are particularly common in anti-CTLA-4 therapy (41). Isolated upper GI inflammation (gastritis, gastroenteritis, or enteritis) occur with a frequency of more than 10% (13,42,43).

As the intestinal symptoms caused by ICIC are diverse, an accurate differential diagnosis is needed before a final diagnosis can be made, except for other etiologies, such as medications, infections, and IBD. The guidelines recommend stool testing for pathogens in patients who present with moderate to severe diarrhea, abdominal pain, fever, or GI bleeding after ICIC therapy. However, infectious factors may coexist with ICIC and common pathogens include cytomegalovirus, *Clostridium difficile*, *Salmonella* and *Candida* (12,44-46). ICIC and IBD have similar clinical and histologic features, and in some circumstances, their endoscopic and histological findings, such as patchy or segmental distribution and crypt architecture irregularities (40), are nearly superimposable (47). In addition to having similar clinical and endoscopic manifestations, ICIC and IBD share certain similarities in terms of pathogenesis. Both diseases increase regulatory cytokines (e.g., INF-γ and IL-17) at the mucosal level (24). Further, CTLA-4, PD-1/PD-L1, and the gut microbiome also play important roles in intestinal immunity in both IBD and ICIC patients (48). In a mouse model of IBD, PD-1 protein was found to be protective against colitis (22). In humans with Crohn's disease (CD), intestinal APCs do not express PD-L1 (49). Conversely, several CTLA-4 polymorphisms are known to enhance the risk of developing both CD and ulcerative colitis (UC) (50). Given the above-mentioned similarities in the clinical manifestations, histology, immunology, and pathogenesis of ICIC and IBD, the current relatively mature treatment regimen for IBD may provide treatment options for ICIC.

Treatment

The treatments for ICI-related GI issues are tripartite and comprise: withholding ICIs to prevent further toxicity; inducing immunosuppression to reduce inflammatory changes; and providing supportive therapy to address GI complications. Treatment approaches vary greatly; however, it is widely agreed that ICIC therapy should be initiated, and ICI medication should be discontinued if the severity of symptoms exceed grade 2 (51). We discuss the clinical drugs used for the treatment of colitis, as well as their modes of action and mechanisms in the following sections.

CSs

CSs (prednisone 1–2 mg/kg/day or equivalent) are often the first line of treatment for grade 2 or above colitis (5). Additionally, given the characteristics of nocturnal diarrhea in ICIC patients, the divided administration of steroid hormones may be considered in clinical practice. CSs inhibit

the development of dendritic cells and cause activated T cells to undergo apoptosis, suppressing both the innate and adaptive immune systems (52). Further, CSs also inhibit the production of proinflammatory cytokines such as IL-2 and IFN-γ from activated T cells (53). CSs have been shown to increase the surface expression of PD-1 in both $CD4^+$ and $CD8^+$ T cells and suppress their functions in mouse models (54). This suggests that systemic CS treatment could be used for ICICs. It should also be noted that the high-dose and long-term treatment of CSs raises the risk of side effects such as infections, osteoporosis, and decreased glucose tolerance (55), and recent research suggests that high-dose steroids may hinder optimal antitumor responses (56,57). The use of mesalazine and topical steroids as a therapeutic strategy in addition to systemic steroids to minimize the side effects of high-dose hormone use has also been reported

In addition, it is important to consider the patients with steroid-refractory or steroid-resistant ICIC. Steroid-refractory ICIC requires the use of immunosuppression due to an initial non-response to CSs, while steroid-resistant ICIC requires the use of immunosuppression after the initial response and the continued use of systemic steroids (58). In a series of retrospective studies of patients with ICI-related diarrhea/colitis (30,33,59), only approximately half of the patients treated with CSs experienced symptom relief. However, in some situations, CSs are unable to control symptoms, and in the absence of more aggressive management, diarrhea or colitis may continue, worsen, or even become life threatening. When symptoms improve, patients should be gradually weaned off CSs over 4 to 6 weeks (5); however, symptom recurrence may occur during the decrement process. Overall, 2% of patients require additional immunosuppressive therapies other than steroids, which may last for several months, and management is challenging.

Diarrhea and colitis are the most common irAEs (58). Approximately 30–60% of ICI-associated diarrhea/colitis patients have a tendency to be resistant to first-line CSs, showing no response to high-dose steroids within 72 hours or no complete remission within 1 week (30), which is related to the expression level of TNF-α. Given the function of TNF family proteins in response to steroid treatment, the following points cannot be ignored: (I) mucosal TNF-α expression levels are negatively correlated with susceptibility to CS (55); and (II) patients with CS-resistant irAE colitis exhibit elevated expression of IFN-γ signaling genes in their intestinal mucosa (30).

In summary, CS-refractory/resistant ICIC can cause serious conditions that can be fatal if treatment fails (58,60). Thus, further treatments are urgently needed. Due to the morphological and immunological similarities between ICIC and IBD, it has been proposed that biologic therapy be applied to ICIC. The management of CS-refractory/resistant irAEs is a growing challenge, and alternative treatment courses need to be explored. It is currently visible in the clinical practice of IBD, and endoscopic results should be taken into account to identify patients who should receive infliximab (IFX) or vedolizumab (VDZ), rather than waiting for a response to CSs. Current studies have shown that in addition to first-line hormone therapy, IFX and VDZ are the main treatments for steroid-refractory/resident ICIC patients (61,62).

IFX

IFX, a chimeric immunoglobulin G1 monoclonal antibody against TNF, causes immunosuppression. It is a TNF inhibitor that blocks the effects of the proinflammatory cytokine TNF-α. TNF-α signaling plays a significant role in cellular processes. It was first approved to treat UC and CD. In accordance with standard IBD therapies, IFX (5 mg/kg/dose) is administered intravenously to treat CS-resistant irAE colitis. For irAE colitis, the therapeutic response to IFX usually occurs in a few days, and symptoms improve with just one dose (63-65). Some patients need to take a second dose of IFX after two weeks. Evidence shows that the chance of endoscopic and histological remission can be increased, and the risk of recurrence can be reduced if up to three doses (at weeks 0, 2, and 6) are administered (66).

In certain retrospective cohort studies (67,68), patients with IFX-treated CS-refractory irAE colitis have been reported to have remission rates of 54% and 71.4%, respectively. Researchers compared the clinical outcomes of patients with irAE colitis treated with CSs alone to those who received IFX after beginning CS therapy (69). Patients who received IFX after CS therapy experienced a considerably shorter time to symptom relief, suggesting that early IFX administration should be considered. In most published case series, positive results have been reported with TNF-α inhibition, with almost all patients with colitis improving after a single dose of a TNF-α inhibitor. Thus, it is not only beneficial for symptom control but also for shorter hospital stays, which supports the strategy of the early initiation of TNF-α suppression rather than systemic steroid therapy that lasts for months. Notably, before

the initiation of IFX, an infectious workup for human immunodeficiency virus (HIV), tuberculosis, and hepatitis should be performed to exclude latent infection.

VDZ

VDZ can be used in cases where IFX is contraindicated or ineffective, and is the first choice when anti-TNF agents are contraindicated. VDZ is an immunoglobulin G monoclonal antibody that binds to α4β7 integrin in activated T cells. By preventing memory T cells from sticking to and penetrating the intestinal wall (70), it also hinders the entry of activated T cells into intestinal tissue by blocking their interaction with mucosal address in cell adhesion molecule-1 (MAdCAM-1), which is specifically expressed in intestinal vascular endothelial cells (71,72). Abu-Sbeih *et al.* investigated the effects of VDZ on irAE colitis that was resistant to CSs and/or IFX (73). The remission rate of VDZ was 67% in patients who received IFX before, and 95% in patients who did not receive IFX, and no side effects were noted. The exact duration of VDZ has not been determined; however, similar to IFX, a study has found that the risk of recurrence will be reduced and the chance of endoscopic or histologic remission will be increased if up to three doses (at weeks 0, 2, and 6) are administered (23). Infectious testing, such as HIV and tuberculosis testing, should also be undertaken to exclude possible infection before VDZ treatment is initiated. Notably, VDZ is a gut-specific agent, and it is unclear whether VDZ can be used to treat other non-GI-related irAEs (74,75).

VDZ can specifically limit the interaction of leukocytes with the intestinal vasculature and prevent the influx of inflammatory cells, which mediate the inflammatory process in immune-related colitis (76). Because of its highly gut-selective mechanism, long-term VDZ treatment has a remarkable safety profile (77), and its administration in clinical practice may lead to fewer systemic immunosuppression and adverse effects. An observational study comparing VDZ and IFX in the treatment of ICIC reported similar response rates in patients treated with the two monoclonal antibodies, but the VDZ group had a longer duration of clinical remission. Moreover, VDZ was linked to shorter CS exposure. Further, compared to patients receiving IFX alone, those receiving VDZ monotherapy had better results and a decreased rate of cancer progression. A notable decrease in the infection rate was also detected in the VDZ group (75).

Both VDZ and IFX have similar efficacy, but the safety profile of VDZ is greater than that of IFX. Choosing between IFX and VDZ for CS-refractory patients is challenging due to limited data, but in general, IFX should be avoided in patients with confirmed or suspected infections, or other contraindications to TNF-α inhibitors, while extreme caution should be exercised when considering whether to administer VDZ to patients with GI tract cancers, metastasis, or GI tract infections (78). The use of VDZ is attractive in this patient population due to its safety profile, but IFX may achieve faster remission based on its efficacy in acute, hospitalized patients (79,80).

Other therapeutic agents

There are not enough well-established alternative therapy choices for patients who do not respond to normal standard care (81). New therapeutic agents for treating ICIC include tofacitinib, tocilizumab, ustekinumab, and mycophenolate mofetil (MMF), but these new therapeutic agents are currently available off-label. Using the JAK inhibitor tofacitinib, Sasson *et al.* successfully inhibited T-cell function in a patient with refractory ICIC (82). Tocilizumab is an antibody that works by binding to the IL-6 receptor to help lower the amount of proinflammatory cytokines produced (83). Tocilizumab can be safely used to treat ICIC, and has been reported a clinical benefit rate of 84%. It should be noted that clinical trials have reported intestinal perforation with tocilizumab, especially in patients with GI ulcers and long-term hormone therapy, where the risk of intestinal perforation is increased (84). Therefore, tocilizumab should be administered carefully in patients with a history of long-term steroid hormone use and those with ulcerative lesions.

Ustekinumab, a monoclonal antibody facilitates mucosal healing by blocking a crucial part of the inflammatory helper T-cell pathway. Two cases have reported that Ustekinumab was effective in the patients who were initially refractory to CSs, IFX, and VDZ (85). MMF inhibits inosine-50-monophosphate dehydrogenase (IMPDH) and exerts immunosuppressive effects by preventing T-cell and B-cell multiplication. Mir *et al.* examined 11 patients with irAE colitis who were treated with MMF in combination with CSs, and reported that seven of these patients had no recurrence during CS reduction, and the remaining patients responded strongly to IFX (86). Calcineurin inhibitors bind to calcineurin by forming an intracellular complex with FK506-binding protein 12, inhibiting the release of cytokines and

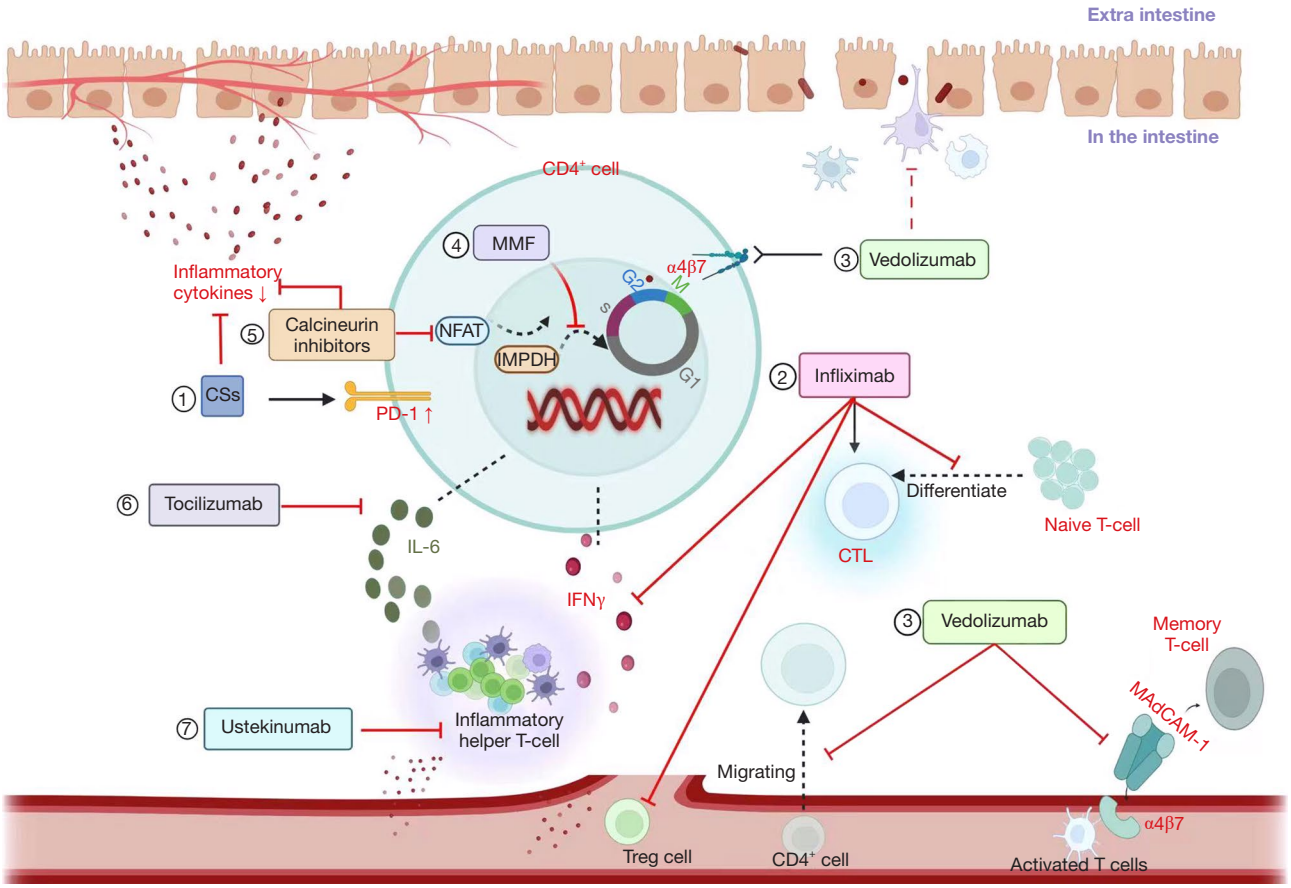

Figure 1 The mechanism of CSs, biologics, and other therapeutic agents for ICIC. ①, CSs increase PD-1 expression on the surface of CD4+ T cells, and inhibit the release of inflammatory cytokines. ②, infliximab increases CTL activity, reduces regulatory T-cell function, suppresses naive T cells from differentiating into CTLs, and blocks the effects of the proinflammatory cytokine TNF-α. ③, vedolizumab specifically binds to α4β7 integrin in activated T cells, preventing memory T cells from sticking to and infiltrating the bowel wall, and inhibits the entry of activated T cells into intestinal tissue by blocking the interaction with MAdCAM-1. ④, MMF reversibly and selectively inhibits IMPDH, and arrests lymphocyte proliferation from the G1 to S phases. ⑤, calcineurin inhibitors prevent the translocation of the nuclear factor of activated T cells into the nucleus, and reduce the expression of inflammatory factor genes. ⑥, tocilizumab works by targeting the IL-6 receptor, and helps to decrease the production of proinflammatory cytokines. ⑦, ustekinumab promotes mucosal healing by blocking a key component of the inflammatory helper T-cell pathway. CS, corticosteroid; ICIC, immune checkpoint inhibitor-associated colitis; MMF, mycophenolate mofetil; NFAT, nuclear factor of activated T cells; MAdCAM-1, mucosal address in cell adhesion molecule-1; IMPDH, inosine-50-monophosphate dehydrogenase; PD-1, programmed cell death protein-1; IL-6, interleukin-6; IFN-γ, interferon-γ; CTL, cytotoxic T lymphocyte; TNF-α, tumor necrosis factor-α.

exhibiting a robust immunosuppressive effect by inhibiting T-cell activation (87). Kunogi *et al.* reported a case in which symptoms improved following tacrolimus treatment for irAE colitis refractory to CSs, IFX, and VDZ (88).

The mechanisms of CSs, biologics, and other therapeutic agents for ICIC are shown in *Figure 1*.

In summary, CS-refractory/resident patients treated with IFX or VDZ had better remission rates. Therefore, the use of biologics (alone or in combination with CSs) should be explored early in the treatment of high-risk patients and not only as an escalation after a failure to respond to CSs. The early use of IFX or VDZ was significantly related to fewer hospitalizations and a shorter duration of steroid treatment. High-risk patients were chosen primarily based on the severity of the ICIC, response to CSs, and the development of large and deep mucosal ulcerations, as well as extensive

inflammation beyond the left colon (66,89,90). There is growing evidence that endoscopy may not only confirm an ICIC diagnosis but also provide insights into the optimal immunosuppressive regimen (33,42,59,91). Mooradian *et al.* reported that the Mayo Endoscopic Score (MES) was significantly higher in patients who required IFX than those who did not, while those with a MES of zero rarely required further immunosuppression. They also found no correlation between the intensity of clinical symptoms and the MES. According to these findings, similar to IBD, endoscopic characteristics can inform clinical judgments more effectively than ICIC patient symptoms alone (92). For ICIC, endoscopy is useful for identifying both high-risk patients and those who may benefit from early biologic use.

In the past, biologics were usually used as second-line treatments after the failure of hormone therapy for ICIC. However, by summarizing the above related mechanisms of the possible occurrence of ICIC and current therapies involving CSs and biologics, we found that CSs and biologics have different targets and affect their respective signaling pathways. Therefore, biologics should not be considered as an alternative and complementary option after the failure of CS therapy, but should be considered as an early treatment. However, the risk of infection caused by the extensive immunosuppressive effects of hormones combined with biologics also requires attention. At present, it is still uncertain whether all patients will benefit from the early use of biologics; thus, the precise identification of patient groups that can benefit from early biologics treatment should receive more attention, and achieving optimal clinical outcomes through more precise and personalized treatment strategies is a challenge that should be addressed in the future.

Microbiome alteration and fecal microbiota transplantation

The gut microbiome has been extensively studied in IBD, and changes in microbiome patterns associated with inflammatory activity include a decrease in the abundance of microorganisms, including *Mycobacterium anisopliae*, *Verrucomicrobiae*, and *Bifidobacteriaceae*, and an increase in the abundance of *Clostridiaceae*, *Enterobacteriaceae*, *Enterococci*, and *Streptococci* (93-96). Similarly, the gut microbiome plays an important part in the process of ICIC. Recent studies have shown that certain bacteria are associated with the onset and severity of ICIC (97,98). The bacterial taxa in the ICIC are predominantly *Clostridium difficile* and *Escherichia coli* with a few anaplastic and warty microorganisms (99). Therefore, there is a great deal of overlap between the microbiome characteristics of ICIC patients and those of IBD patients. Gut microecological dysregulation can trigger intestinal inflammation (100,101), and the microbiome plays an important role in the tumor response to immunotherapy, and the risk of ICIC development (102).

Given the critical role that ecological dysbiosis plays in ICIC, fecal transplants have been considered as a potential treatment for specific patients. Fecal transplants can restore the normal gut microbiota and reduce mucosal inflammation. To date, international guidelines have recommended it for the treatment of recurrent *C. difficile* colitis, but there is insufficient clinical evidence about its use in the treatment of ICIC. There are some case reports of successful fecal transplantation for the treatment of refractory and severe ICIC; however, there are no relevant data on the timing of the treatment or complications (103,104). Thus, further studies need to be conducted in the future to provide more adequate evidence for its clinical use.

Conclusions

The use of ICIs has revolutionized the prospects of tumor therapy and improved the prognosis of many patients. However, ICIs can also lead to irAEs, the most common of which is ICIC, which can severely reduce the quality of life of patients, and result in the termination of immunotherapy. Biologics are currently recommended for the treatment of ICIC, but are usually used as a supplement after the failure of first-line CS therapy. Increasing data suggest that patients with irAE colitis respond favorably to biologics, and that patients with CS-resistant/refractory enterocolitis can benefit from the early use of biologics. Biologics (alone or in combination with CS) should be considered as an early therapy option for high-risk patients rather than just as an escalation after a failure to respond to CSs. In terms of the selection of biologics, IFX and VDZ have similar overall response rates, but IFX has a faster onset of action than VDZ. Conversely, VDZ can cause IFX resistance or have contraindications to its use, but it is safe due to its high intestinal selectivity and can be used as a prophylactic agent. However, early use of biologics is still in the clinical practice phase with limited retrospective studies. There will need more prospective research in the future. The management of patients with ICIC needs to be individualized and refined. The gut microbiota is an emerging area that can provide information about the mechanisms and potential

therapeutic targets of ICIC.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-2150/rc

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-2150/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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