Gastrointestinal Tract

REVIEW ARTICLE

# Immune checkpoint inhibitors induced colitis: Diagnosis and treatment in the era of biological agents

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**ABSTRACT**

Pharmaceutical agents in the immune check-point inhibitors class contribute decisively to treating patients with metastatic carcinoma. Having immunomodulatory activity, these drugs predispose to the occurrence of side effects from the digestive tract, ranging from uncomplicated diarrhea to the development of life-threatening colitis, which resembles ulcerative colitis. Early diagnosis and therapeutic intervention are necessary in these patients to avoid undesirable progression. This review summarizes recent data on the etiopathogenesis, diagnosis, and therapeutic management of immune check-point inhibitors induced colitis. Recent advances include the role of the gut microbiome in the pathogenesis of the disease, and the emerging therapeutic strategies include the administration, in addition to the established biologic agents infliximab and vedolizumab, tocilizumab, ustekinumab, mycophenolate mofetil, and calcineurin inhibitors. The precise place of these agents in treating patients is expected to be more accurately determined when the etiopathogenetic mechanisms of this colitis are adequately elucidated.

**Key words:** immune checkpoint inhibitors, colitis, biologic agents, vedolizumab, infliximab, inflammatory bowel disease

## INTRODUCTION

Immune checkpoint inhibitors (ICIs) are essential immunomodulatory drugs with potent antineoplastic activity and a broad application in oncology. Among the side effects that may occur during treatment, Immune checkpoint inhibitor induced colitis (CIC) is the most important regarding the clinical symptoms and therapeutic management. Risk factors for developing this complication include the gut microbiome, any pre-existing autoimmune disorders, and the type of neoplasm. CIC can lead to severe complications, which can sometimes become life-threatening.[1,2] The importance of the gastroenterologist's participation in multidisciplinary patient management is becoming evident since it is impossible to continue antineoplastic therapy without previous colitis remission.

ICIs were first introduced into clinical practice in 2014. Since then, these drugs have become fundamental anticancer agents in treating many malignant tumors. It is well known that immune checkpoints, which regulate immune responses to prevent autoimmunity, are "exploited" by cancer cells to escape being killed. The discovery of the PD-1/PD-L1 and CTLA-4 proteins (programmed cell death-1, programmed cell death-ligand 1, and cytotoxic T lymphocyte antigen-4, respectively) has contributed decisively to the application of cancer

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immunotherapy. PD-L1 exists on the surface of antigen-presenting cells and tumor cells, resulting in self-tolerance promotion and autoimmunity attenuation after interacting with PD-1. CTLA-4 is expressed on CD4+/CD8+ T cells, B-cell subsets, and thymocytes, suppressing T-cell activity. Treatment with ICIs causes restriction of suppressive signals of cytotoxic CD8+ T-cells, resulting in inhibition of PD-1, PD-L1, and CTLA-4. PD-1/PD-L1, CTLA-4, TIM-3, and CD47/SIRP□ are regulated by circRNAs, through serving as ceRNAs. CircRNAs may regulate the expression of two or more immune checkpoints at the same time. This regulation means that circRNAs mitigate the resistance by controlling the other immune checkpoint when the tumor develops resistance to one ICI.[3] Research efforts are directed today toward new checkpoints such as TIM-3, VISTA, B7-H3, BTLA, and TIGIT. Moreover, several biomarkers, such as tumor mutation burden, Interferon-γ, intestinal microbiome, and extracellular matrix characteristics, are used in predicting response to immunotherapy with ICIs.[4]

In January 2024, the US Food and Drug Administration approved 11 drugs, each with particular indications. The inhibitors of PD-1 (nivolumab, pembrolizumab, cemiplimab), PD-L1 (atezolizumab, durvalumab, avelumab) and CTLA-4 (ipilimumab, tremelimumab), as well as the LAG-3 inhibitor relatlimab, are now widely used. The list of ICIs is gradually expanding. Jeddeo P *et al.*, in a recent presentation, evaluated the 43 FDA-approved January 2024 indications for 11 ICIs. The indications per drug ranged from 2 (retifanlimab, toripalimab, and tremelimumab) to 35 (pembrolizumab). Fifteen (43%) indications were non-overlapping. Pembrolizumab had 11 non-overlapping indications (*e.g.*, breast, cervical, and urothelial cancers). The non-overlapping indications of all other drugs fluctuated between 0 and 2.[5] Table 1 lists the currently approved ICIs, the year of approval, and the indications for administration. The present article introduces colitis caused by immune checkpoint inhibitors, focusing on the pathogenesis, diagnosis, treatment, and prognosis of the disease.

## EPIDEMIOLOGY

It has been estimated that the overall incidence of diarrhea is 30.2%–35.4% for CTLA-4 inhibitors and 12.1%–13.7% for PD-1/PD-L1 inhibitors, while the incidence of colitis ranges from 5.7% to 39.1% for CTLA-4 inhibitors and 0.7% to 31.6% for PD-1/PD-L1 inhibitors. The combination of PD-1/PD-L1 and CTLA inhibitors could result in a 40.4% incidence of diarrhea. The metaanalysis by Tandon P *et al.* included 18 studies: 6 studies (1537 patients) with PD-1 inhibitors and 12 studies (3116 patients) with CTLA-4 inhibitors. All-grade diarrhea was 13.7% for anti-PD-1 and 35.4% for anti-CTLA-4. All-grade colitis was 1.6% for anti-PD-1 and 8.8% for anti-CTLA-4. The treatment discontinuation rate was numerically higher for anti-CTLA-4 therapy than for anti-PD-1 therapy. Two studies comparing combination immunotherapy with anti-CTLA-4 therapy alone showed that the relative risk of all-grade diarrhea and colitis with combination therapy was 1.31. In contrast, with anti-CTLA-4 alone, it was 1.21, suggesting that diarrhea and colitis are common complications of ICI treatment, being more frequent after treatment with CTLA-4 inhibitors.[6]

Another metaanalysis by Wang *et al.* included 34 original ICIs studies containing 8863 patients. Seventeen studies compared cases in different tumor types. Total grade, grade 3–4 (severe) colitis, and grade 3–4 (severe) diarrhea cases were pooled. The overall incidence during ipilimumab monotherapy was 9.1% for all-grade colitis, 6.8% for severe colitis, and 7.9% for severe diarrhea. Incidence was lower during PD-1/PD-L1 inhibitor monotherapy, with 1.3% for all-grade colitis, 0.9% for severe colitis, and 1.2% for severe diarrhea, while the combination of ipilimumab and nivolumab resulted in the highest incidence of all-grade colitis (13.6%), severe colitis (9.4%) and severe diarrhea (9.2%) among ICIs. Among patients with melanoma, nonsmall cell lung carcinoma, and renal cell cancer, the incidence of colitis and diarrhea with PD-1/PD-L1 inhibitor monotherapy did not differ significantly. The incidence of severe colitis was similar with ipilimumab monotherapy at 3 mg/kg and 10 mg/kg (7.1% *vs.* 5.1%, respectively) but significantly higher for severe diarrhea at 10 mg/kg (11.5% *vs.* 5.2%). The incidence of immune-related colitis and severe diarrhea was higher with regimens containing ipilimumab compared with PD-1/PD-L1 inhibitors. There was no significant difference in immune-related colitis between different tumor types with PD-1/L1 inhibitors.[7]

In the metaanalysis of Nielsen *et al.*, it was estimated that the incidence of diarrhea and colitis caused by anti-PD-1/PD-L1 antibodies was 10% and 2%, respectively, with no clinically significant differences between the compounds. The CTLA-4 inhibitor, ipilimumab, caused diarrhea and colitis in 33% and 7% of patients, respectively, while the incidence of diarrhea and colitis after combining ipilimumab with nivolumab was 21%–37% and 4%–8%, depending on the regimen. The incidence of all grades of diarrhea after ICI in combination with chemotherapy or Tyrosine Kinase inhibitors (TKIs) was high (17%–56%), while only 0.5% of patients developed severe (≥ grade 3) colitis. The main patterns of histopathological presentation after monotherapy or combination therapy with PD-1/CTLA-4 inhibitors were acute and chronic active colitis

**Table 1: Food and Drug Administration approved immune checkpoint inhibitors**

| Checkpoint inhibitor and generic name | Date of first FDA approval | # of total indica-tions | # of Mon-overlapping indica-tions | # of indications overlapping with > 3 other drugs | Indication(s) |
|---|---|---|---|---|---|
| Ipilimumab (Yervoy) **Anti–CTLA-4** | Mar 2011 | 8 | 0 | 4 | Melanoma<br>Renal cell carcinoma<br>Microsatellite instability–high cancers |
| Pembrolizumab (Keytruda) **Anti–PD-1** | Sep 2014 | 35 | 11 | 4 | Melanoma<br>Metastatic NSCLC<br>Head and neck squamous cancers<br>Gastric adenocarcinoma<br>Urothelial cancer<br>Hodgkin lymphoma<br>Mismatch repair–deficient solid tumors |
| Nivolumab (Opdivo) **Anti–PD-1** | Dec 2014 | 18 | 2 | 4 | Melanoma<br>Metastatic NSCLC<br>Head and neck squamous cancers<br>Gastric adenocarcinoma<br>Urothelial cancer<br>Hodgkin lymphoma<br>Hepatocellular carcinoma<br>Renal cell carcinoma |
| Cemiplimab (Libtayo) **Anti–PD-1** | Sep 2018 | 4 | 1 | 1 | Cutaneous squamous cell carcinoma |
| Atezolizumab (Tecentriq) **Anti–PD-L1** | May 2016 | 7 | 1 | 2 | Small cell lung cancer<br>Urothelial cancer<br>Breast cancer |
| Avelumab (Bavencio) **Anti–PD-L1** | Mar 2017 | 4 | 0 | 1 | Merkel cell carcinoma<br>Urothelial cancer<br>Renal cell carcinoma |
| Durvalumab (Imfinzi) **Anti–PD-L1** | May 2017 | 5 | 0 | 1 | Small cell lung cancer (stage 3)<br>Urothelial cancer<br>Breast cancer |
| Tremelimumab (Imjudo) **Anti–CTLA-4** | Oct 2022 | 2 | 0 | 1 | Unresected Hepatocellular carcinoma<br>Metastatic non-small cell lung cancer, without EGFR or ALK mutations |
| Retifanlimab (Zynyz) **Anti–PD-1** | Mar 2023 | 2 | 0 | 0 | Merkel cell carcinoma |
| Dostarlimab (Jemperli) **Anti–PD-1** | Jul 2023 | 4 | 0 | 1 | Advanced endometrial cancer |
| Toripalimab (Loqtorzi) **Anti–PD-1** | Oct 2023 | 2 | 0 | 0 | Nasopharyngeal carcinoma |

FDA: Food and Drug Administration

and microscopic colitis. Extended treatment options include combinations of ICI and chemotherapy/TKI with a high incidence of diarrhea and a low incidence of colitis.[8]

Oliveira *et al*., in a recent metaanalysis, included 96 studies with 52,811 patients. Nonsmall cell lung cancer involved 28, and malignant melanoma, 15 studies. Ipilimumab had the worst ranking (SUCRA 14% and event rate 848 per 10,000 patients), while atezolizumab had the best (SUCRA 82% and event rate 119 per 10,000 patients).[9]

The timing of the onset of colitis ranges from a few days after the start of treatment to several weeks or months afterward, as well as after the end of treatment, depending on the type of ICI. ICI-induced colitis can occur at any time, such as at the start of treatment or after the end of treatment.[10–12] Thus, colitis caused by CTLA-4 inhibitors occurs later than that caused by PD-1/PD-L1 inhibitors. The median time to onset of ipilimumab-induced colitis was 6 to 7 weeks after 2-3 infusions.[13] Besides, the onset of CIC occurs significantly earlier in patients receiving combination therapy with ICIs. In addition, it is influenced by other types of treatments, including prior cancer therapy, antibiotics, and non-steroidal anti-inflammatory drugs.[14] Deaths are more frequent as long as anti-CTLA-4 agents are used (1.08%), followed by anti-PD-L1 agents (0.38%) and anti-PD-1 therapies (0.36%). Most deaths

due to anti-CTLA-4 treatment are due to colitis, while fatalities due to anti-PD-1 and anti-PD-L1 are due to pneumonitis, myocarditis, and hepatitis.

## PATHOGENESIS

Although much progress has been made, the mechanisms involved in the pathogenesis of CIC are still unclear. It has been suggested that such mechanisms could include T-cell hyperactivation, excessive lymphocyte infiltration, and increased circulating memory T cells.[15] In patients with severe CIC, significant infiltration of CD4+ T cells and CD8+ T cells is the predominant feature. This CD4+ T cell infiltration was mainly observed in patients treated with anti-CTLA-4, whereas CD8+ T cell infiltration was observed primarily in anti-PD-1-induced colitis.[16] Moreover, in patients with CIC, differentiation from CD8+ tissue-resident memory T cells to cytotoxic T lymphocytes occurs. It was suggested that CD8+ tissue-resident memory T cells in the normal colon induce CIC and that their activation causes the subsequent assembly of CD4+ and CD8+ T cells. Besides, lymphoid cells have been regarded as critically effective cells in the gastrointestinal mucosa, as CIC's severity has been correlated with the growing mucosal number of group 3 innate lymphoid cells.[17] Thomas *et al.* recently argued that circulating T cells and epithelial-immune crosstalk cells play an essential role in PD-1/CTLA-4-dependent tolerance and barrier function, representing potential future therapeutic targets.[18]

He *et al.* performed multicentre single-cell transcriptomics and proteomics to define contributing populations of CIC biopsies from patients with predominantly steroid experience. They identified CD4+ resident memory and molecular vascular vascular address cell adhesion molecule1+ endothelial cells as "targets" in specific subgroups of patients with CIC. Interestingly, they also observed that patients with CIC, compared to ulcerative colitis, had impaired stroma metabolism, affecting epithelial cell survival and inflammation. Furthermore, epithelial cells upregulated the integrin α4β7 ligand molecular vascular adhesion molecule1, which might explain the good response to the anti-integrin biological agent vedolizumab.[19]

A mechanistic understanding of CIC cannot be fully achieved because colitis cannot be reproduced in mice after the administration of ICIs. However, Lo *et al.* reported that this obstacle can be overcome by using mice harboring the microbiota of wild-caught mice, which develop overt colitis following treatment with anti-CTLA-4 antibodies. Intestinal inflammation is induced by direct activation of CD4+ T cells producing IFNγ and depletion of peripherally induced regulatory T cells. This work proposes a novel strategy to mitigate intestinal CIC while preserving the antitumor stimulatory effects of CTLA-4 blockade.[20] Animal models without immune checkpoints have been used to simulate the immunological effects in patients with CIC. These experimental animals showed significant infiltration of immune cells in various organs and fatal colitis due to increased T-cell activity.[21] Other experimental data suggest that many cytokines are involved in the pathogenesis of CIC. In models of experimental colitis, Song *et al.* observed a significant increase in IL-17.[22] Moreover, Singh *et al.* recently found that IL6 is the key cytokine responsible for many side effects during ICI treatment.[23] Bamias *et al.* described that TNF-like cytokine 1A and its receptor DR3 are upregulated in ICI-mediated colitis.[24]

The inducible gene and expression of proinflammatory cytokines IFN-γ and TNF-α were found to be increased in ICI-related colitis patients.[25] How resident mucosal IFNγ cytotoxic CD8+ T cells expand in patients with CIC is unclear. Gupta *et al.* tracked CIC-bound T-cells in intestinal tissue using multimodal single-cell and subcellular spatial transcriptomics. They found that target occupancy was expanded in the inflamed areas of mucosa. Inflammation cells were mainly CD4+ T cells, follicular helper, and regulatory T cells. They also noticed that IFNγ CD8+ T cells emerged from tissue-resident memory and peripheral populations, indicating possible causal pathways.[26]

Besides, the CXCR3 and CXCR6 chemokine receptor (CXCR9/10 and CXCR16, respectively) genes were highly expressed in the colitis-related T-cell population, upregulating T-cell activity.[27] Finally, three genes (ITGB7, ITGA4, and ITGAE), encoding integrin receptors a4b7 and aEb7, are expressed in CIC-associated T cells, which results in lymphocyte adhesion to the intestinal mucosa.

The gut microbiome also plays a critical role in regulating intestinal mucosal homeostasis through interactions with regulatory T cells.[28] Elkrief *et al.* studied the fecal microbiota profiles from 18 patients with CIC, five of whom were treated with healthy-donor fecal microbial transplantation. They found that CIC was characterized by fecal microbial dysbiosis, which included an abundance of Proteobacteria. Five patients received healthy-donor fecal microbial transplantation, with improvement in four patients. They concluded that patients with CIC have a distinct microbiome at the time of CIC onset.[29]

Finally, it is unknown if ICIs therapy increases the risk of pouch-related complications in patients with ulcerative colitis after ileal-pouch anal anastomosis.

Karine *et al.* recently described that pembrolizumab therapy was not associated with severe gastrointestinal immune-related adverse events or pouch-related complications.[30]

## DIAGNOSIS

Clinicians should suspect the existence of CIC as long as a patient treated with ICIs presents with diarrhoeal syndrome with or without blood. Early detection of the disease is critical for the patient because there is always the possibility that the disease may be significantly aggravated, leading even to death due to the development of toxic megacolon or intestinal perforation, which is more frequently seen in patients receiving ipilimumab therapy.

The National Cancer Institute categorizes CIC into five grades based on the common terminology criteria for adverse events (CTCAE), which solely rely on the severity of symptoms (Table 2). Grade 1 indicates diarrhea with less than four bowel movements per day without other symptoms. In comparison, grade 2 means more than four daily bowel movements with blood and mucus and symptoms such as abdominal pain. The clinical picture may be so severe as to require surgical resection of the colon.[31] It is important to emphasize that CIC shares several clinical, histological, biological, and therapeutic features with inflammatory bowel disease.

The diagnosis is based on a detailed history, clinical picture, and detailed objective examination, and it is confirmed endoscopically and histologically. The clinician must use the CTCAE scoring system to categorize the severity of the condition and plan the diagnostic test. From the outset, an infectious origin of the diarrhea should be ruled out through appropriate cultures and parasitological stool tests. Testing all patients for evidence of *Clostridioides difficile* toxin A and B is essential. The American Gastroenterological Association recommends early screening for fecal calprotectin determination. A complete check of liver and renal function should be performed, as well as a determination of serum markers of inflammation (erythrocyte sedimentation rate and C-reactive protein). Testing for tissue transglutaminase immunoglobulin A and total IgA is also essential to exclude the possibility of new-onset celiac disease, a complication of ICIs, albeit rare. Finally, because some patients will need to be treated with biological agents, it is necessary to test for latent infection with hepatitis B and C viruses, cytomegalovirus, Epstein Barr, and herpes and to perform a Quantiferon test for latent tuberculosis.

No such biomarker has been established regarding the usefulness of specific biomarkers contributing to the diagnosis of CIC. However, Yokote *et al.* found a significantly higher rate of particular anti-integrin αvβ6 autoantibodies in patients with CIC compared to controls. These autoantibodies were associated with grade $\geqslant$ 3 colitis steroid resistance and disease activity. Therefore, anti-integrin αvβ6 autoantibodies might be candidate biomarkers for the diagnosis, classification, risk management, and monitoring of disease activity in patients with CIC.[33] In a recently published study, Farooqi *et al.* found that elevated levels of specific cytokines, both before and after starting treatment, correlate with specific adverse reactions in patients with pleural mesothelioma receiving ICIs. They found that MIF with fatigue and eotaxin is valuable in predicting colitis development in these patients.[34] Finally, C-reactive protein elevation and leukine-rich α2-glycoprotein could indicate the onset of adverse reactions in patients treated with ICIs in the absence of infectious disease. However, further studies are needed to establish the exact contribution of these biomarkers.[35,36]

Other laboratory examinations, including colonoscopy, imaging techniques, and histology of the large bowel mucosa, are vital for diagnosing and following up patients. Subsequently, these diagnostic modalities are analyzed.

### *Endoscopy*

Endoscopic examination of the colon is the most fundamental examination necessary for detecting and characterizing colitis. To perform it, the gastroenterologist acts in the same way as in the case of an outbreak or first attack of ulcerative colitis, taking into account the general condition of the patient and the severity of the lesions they detect at the time of the endoscopy. As in inflammatory bowel disease, the seriousness of the endoscopic lesions does not always parallel the severity of the clinical symptoms and vice versa. There is disagreement on whether endoscopy should be performed in all patients. Based on the previous statement, the author believes that colonoscopy and multiple biopsies of affected or non-patient colonic mucosa should be performed. A left colonoscopy is indicated because the left colon is involved in most CIC cases.

Endoscopic findings range from normal mucosa to mild, moderate, or severe inflammatory lesions such as swelling, redness, ulceration, and superficial or deep ulcers in tissue continuity or skip lesions. Deep ulcers are a high-risk sign for the patient, indicating the need to use biological agents as the treatment of choice.[37]

The categorization of endoscopic findings follows the

**Table 2: Standard terminology criteria for adverse events.[32]**

| Grade | Diarrhea | Colitis |
|---|---|---|
| 1 | Increase of stool frequency < 4/day over baseline; mild increase in ostomy output compared with baseline | Asymptomatic; clinical or diagnostic observations only; intervention not indicated |
| 2 | Increase of stool frequency 4–6/day over baseline; moderate increase in ostomy output compared with baseline | Abdominal pain; mucus or blood in stool |
| 3 | Increase of stool frequency ⩾ 7/day over baseline, incontinence, need for hospitalization, and limiting self-care activity of daily living; severe increase in ostomy output compared with baseline | Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs |
| 4 | Life-threatening consequences; urgent need for intervention | Life-threatening consequences; urgent intervention indicated |
| 5 | Death | Death |

grading of lesions in patients with ulcerative colitis (Mayo scores 0 to 3 depending on the severity of the lesions), although the description of the Mayo score's individual parameters is beyond the scope of this review.

Colonoscopy is also valuable in monitoring patients after clinical remission to resume treatment with ICIs. It is well established that in patients with inflammatory bowel disease, monitoring disease activity through sequential determinations of stool calprotectin levels is particularly helpful. Fecal calprotectin concentration may also serve as a noninvasive biomarker to predict endoscopic and histologic remission in patients under treatment for CIC. However, more data are awaited to define the precise role of this marker of inflammation.[38]

### Radiology

Imaging examinations can also contribute generously to demonstrating CIC and other complications of ICI treatment.[39] So, regarding the contribution of abdominal computed tomography in the diagnosis of CIC, as in the case of inflammatory bowel disease, the findings are non-specific and include the demonstration of possible dilatation of the colon with thickening of the wall and congestion of mesenteric vessels. Abdominal computed tomography scanning is required in case of suspicion of serious complications such as toxic megacolon, perforation of the bowel, or intra-abdominal abscess. Computed tomography scanning may indicate the presence of two different types of colitis: diffuse colitis and segmental colitis.[40] Diffuse colitis is characterized by the involvement of a long segment of the colon with mucosal enhancement, bowel wall thickening, fluid in the bowel lumen, and mesenteric vessel engorgement.

In contrast, focal colitis can be seen in a bowel segment with pre-existing diverticulosis (segmental colitis).[41] Findings in focal colitis include thickening of the bowel wall, but it is limited to a single site, with mucosal enhancement and pericolic fat stranding. On positron emission tomography/computed tomography scan, an FDG uptake within the mucosa of the colon segment that is involved can be seen.

Mekki *et al.* investigated the role of different imaging techniques in the detection of side effects during treatment with ICIs (nivolumab and pembrolizumab) of 53 patients with malignant melanoma and lung cancer. Seventy-four medical imaging procedures were analyzed, and 55 treatment side effects were detected. The overall rate of side effects detection was 74%. The individual detection rate was positron emission tomography with 18F-fludeoxyglucose integrated with computed tomography: 83%, magnetic resonance imaging: 83%, computed tomography scan: 79%, and ultrasonography: 70%. It is of interest that enterocolitis was detected in all cases ($n = 8/8$). These findings suggest that imaging examinations are an essential diagnostic tool to demonstrate complications in patients receiving ICIs. Furthermore, in addition to assessing response to treatment, imaging examinations can become a guide towards specific management.[42]

### Histology

The histological picture of the colonic mucosa of patients with CIC is characterized by several conditions, including diffuse active colitis, chronic active colitis, microscopic colitis (collagenous or lymphocytic), graft-versus-host disease-like colitis ischemic colitis, and mixed colitis.[43] Most patients have acute inflammatory changes on biopsy with infiltration of the lamina propria with neutrophils, lymphocytes, plasma cells, and eosinophils. Granulomas have also been reported rarely. In the majority of cases, the inflammatory involvement is diffuse.

Isidro *et al.* studied 86 patients with CIC (ipilimumab 14 patients, ipilimumab + nivolumab, 29 patients, nivolumab 20 patients and pembrolizumab 23 patients). The histological lesions recorded included diffuse active colitis, chronic active colitis, lymphocytic colitis, collagenous colitis, graft versus host disease colitis, and mixed colitis. Patients who received ipilimumab were more likely to have active colitis and less likely to have lymphocytic colitis than other patients. Microscopic

colitis was more common in patients receiving nivolumab and pembrolizumab. Chronic active colitis was more common in patients treated with nivolumab. CIC presents medication-specific differences in patterns of injury, which should be considered in the differential diagnosis.[44]

In an interesting study, Tomm *et al.* studied the histological picture of the colon of 30 patients with CIC over time. They found that 37% of the patients had a different histological picture from the initial diagnosis. These patients were more likely to be retreated with (other) ICI compared to patients whose colorectal histological picture did not show a change over time. Interestingly, the observation was that the altered histological picture resembled an inflammatory bowel disease picture. The symptoms of these patients resolved and did not recur despite the absence of maintenance treatment with steroids or other immunosuppressive drugs, suggesting a clear correlation of treatment with ICIs concerning the occurrence of ICI. These findings indicate that a significant proportion of patients demonstrate a differential histological pattern during follow-up without implying that the initial histological diagnosis should necessarily be altered.[45]

### *Differential diagnosis*

The diagnostic test should include excluding Cytomegalovirus infection by taking biopsies from various parts of the colon, including the rectosigmoid, for microscopic lesions, as well as biopsies from the duodenum to exclude the possibility of celiac disease since patients treated with ICIs may develop celiac disease as a side effect of treatment. Because the overwhelming proportion (98%) of CIC cases involve the left colon, recto sigmoidoscopy with the flexible sigmoidoscope can be considered adequate. The exclusion of Clostridium difficile infection should also be kept in mind. In support of this assumption, Vuillamy *et al.*, in a retrospective multicentre study, attempted to associate Clostridium difficile infection with CIC in 18 patients receiving anti-CTLA-4 (4 patients), anti-PD-1 (11 patients), and anti-PD-1 in combination with anti-CTLA-4 (3 patients) in patients with malignant melanoma. The results showed that Clostridium difficile infection can be isolated or can complicate or reveal CIC, having many features in common with ulcerative colitis or Crohn's disease.[46] The authors of this review again emphasize the need to perform the necessary tests to detect *Clostridium difficile* infection in all patients with diarrhea or CIC related to ICI therapy.

## TREATMENT

The treatment goals are the rapid reversal of symptoms, avoidance of complications, and, when possible, the possibility of continuing or reintroducing immunotherapy. The type and intensity of treatment depend on the severity of the colitis/diarrhea. The severity of the endoscopic picture of the colonic treatment should be considered when planning the type of treatment for the particular patient. From the outset, what is also true in managing patients with inflammatory bowel disease should be emphasized: managing ICI-induced colitis requires an early multidisciplinary approach. Before starting treatment, it is necessary to confirm the diagnosis using clinical and laboratory parameters (clinical presentation, laboratory markers, endoscopic and histologic examination). Subsequently, and based on these criteria, it should be decided whether or not the patient should be hospitalized. The initial endoscopic assessment of the condition of the colon is of great importance for the planning of treatment, especially treatment with biological agents.[47]

The multidisciplinary approach is paramount for the favorite outcome of the patients with CIC. In a relevant retrospective study, Bonanno *et al.* investigated the clinical relevance of an interdisciplinary approach to patients with immune-mediated diarrhea and colitis. They found that in patients with advanced nonsmall cell lung cancer who received sequential treatment with ICIs, either as a single agent or in combination with chemotherapy, they were predominantly female, belonged to the PD-L1 expression, and had a more prolonged overall survival. Adopting a multidisciplinary approach was associated with increased use of diagnostic tools such as fecal calprotectin determination, colonoscopy, and gastroenterological evaluation. Furthermore, the multidisciplinary approach resulted in a significant reduction in grade 3 regression and relapse incidence. Finally, hospitalization decreased from 17.2% to 3.8%.[48]

Supportive care is applied to patients with grade 1 CIC. Treatment consists of adequate hydration with oral fluids and easily digestible low-fat food intake. As long as symptoms do not worsen, ICI treatment can be continued. Antidiarrhoeal medication should be taken with caution because of the risk of toxic megacolon. Urgent rectosigmoidoscopy is considered necessary even if there are no findings from the rectosigmoid, followed by total colonoscopy and ileoscopy in patients with persistent symptoms. Determination of markers of inflammation in stool and serum is considered necessary even in patients with grade 1 CIC. However, some consider endoscopy essential in CIC grade 2 and above patients. However, other societies reserve endoscopic evaluation (colonoscopy or flexible sigmoidoscopy) for patients with grade 2 or higher colitis. It should be emphasized that in most patients, the course of CIC is relatively mild, responding satisfactorily to corticosteroid therapy. A smaller proportion of patients, most

commonly those treated with T-cell cytotoxic antigen-4 inhibitors, may have a more severe course of colitis, even life-threatening complications. These patients require early diagnosis, endoscopic evaluation, and intensive treatment with high doses of corticosteroids. If corticosteroids are ineffective, biological agents such as rescue therapy are necessary.[49,50]

In patients with grade 2 colitis, treatment with ICIs may be continued temporarily until symptoms return to a grade 1 level. The possibility of permanently discontinuing anti-CTLA-4 agents should always be kept in mind, and anti-PD-1 and anti-PD-L1 therapy may be restarted if the patient resolves to grade 1. Patients with grade 2 colitis should be treated, especially those with fever or signs of dehydration. These patients' treatment involves administering corticosteroids (initial dose of 1 mg/kg/d of prednisone). If symptoms do not improve in 3 or 4 days (the authors expect as many as 7 days), the prednisolone dose increases. If symptoms resolve (colitis grade 1), corticosteroids are gradually reduced. Re-administration of ICIs can be done as long as the dose of corticosteroids is sufficiently reduced. Other guidelines (National Comprehensive Cancer Network) (NCCN) recommend starting biologic agents if there is no improvement on day 4 after starting corticosteroid therapy in parallel with corticosteroids. The AGA recommends the administration of mesalazine or budesonide in patients with grade 2 colitis and mild endoscopic activity with a histologic appearance similar to microscopic colitis. Treatment with ICIs can only be restarted if clinical remission is achieved and the dose of corticosteroids is reduced.

In patients with grade 3 colitis, all the measures taken in patients with grade 2 colitis are generally applied. Still, especially in this category of patients, the possibility of permanent discontinuation of ICI treatment should be seriously discussed. Treatment with anti-PD-1 and anti-PD-L1 can be restarted as soon as the patient has regressed to grade 1. Dehydration and systemic symptoms are appropriately counteracted. The dose of prednisolone may exceed 1 mg/kg/d. If symptoms improve to grade 1 or less, the patient is given oral administration with gradual tapering for 4 to 8 weeks. Biological agents are administered if no improvement is achieved with corticosteroids within one week.

Finally, in patients with grade 4 colitis, definitive discontinuation of ICI therapy and hospitalization is recommended. Otherwise, all treatment guidelines for patients with grade 3 colitis apply. In general, two-thirds of patients with CIC may respond to corticosteroids, while the other third do not respond and need biological agents. The choice of biological agent is left to the gastroenterologist. In general, vedolizumab has a slight advantage over infliximab. After remission, patients do not need to enter a maintenance treatment program.

Regarding the expected results of using corticosteroids and biologic agents in CIC in the metaanalysis of Ding *et al.*, which included 27 studies of patients with any form of colitis/diarrhea (17%), low-grade colitis (3%), high-grade colitis (17%), low-grade diarrhea (13%), and high-grade diarrhea (15%), the following were found: The pooled rates of overall response, response to corticosteroid therapy, and response to biologic agents were 88%, 50%, and 96%, respectively. The pooled incidences of permanent discontinuation and restart of ICIs were 43% and 33%, respectively. Therefore, 50% of patients with CIC respond to corticosteroid therapy, whereas corticosteroid-resistant cases respond to biological agents in a high proportion.[51]

There is little data on the action of other forms of corticosteroids in the literature. In a recent retrospective study by Machado *et al.*, budesonide's role in treating 69 patients with CIC predominantly occurred after combination therapy with anti-PD-1/L1 and anti-CTLA-4 was investigated. The grade of patients with diarrhea was 3, and those with CIC were 2. Budesonide was used as primary therapy at the onset of colitis in 56.5% of patients and as bridging therapy from systemic corticosteroids to biologic agents in 33.3%. A proportion of 45% of patients required adjunctive treatment with biological agents or fecal transplantation. Complete remission of CIC was observed in 75.3%, while 24.6% experienced a relapse. One in 3 patients continued treatment with ICIs. This retrospective study showed that budesonide helps treat and prevent CIC since the remission rates are similar to those achieved with systemic corticosteroid administration, with much fewer side effects. The group of patients requiring long-term corticosteroid administration could be mainly benefit. Budesonide can serve as a bridge from systemic corticosteroid administration to the administration of biological agents. However, the exact role of this drug requires further clinical studies.[52]

Regarding the role of biological agents in treating patients with CIC, the available data indicate that two of them are the most commonly used: vedolizumab and infliximab. The doses of infliximab or vedolizumab are similar to those administered in the induction treatment of patients with inflammatory bowel disease: 5 mg/kg at weeks 0, 2, and 6 for infliximab and 300 mg intravenously at weeks 0, 2, and 6 for vedolizumab. In a recent publication, Joseph *et al.* analyzed the results of patients who received at least one dose of these biologic agents. The results for both infliximab and vedolizumab were excellent. Maintenance of clinical response was seen in 91% of patients receiving infliximab and 86% receiving vedolizumab. There was no difference in the incidence of infections in the two groups. An essential

point of this study is that patients receiving vedolizumab discontinued corticosteroids earlier than infliximab (25 versus 56 days, respectively). Therefore, vedolizumab use is preferable to infliximab.[53] In their study, Dahl *et al.*, including 140 cancer patients treated with infliximab for CIC, found that the rate of complete remission with infliximab was 52% after one dose, increasing to 73% after two or more doses. This suggests that treatment with biological agents should go beyond a single administration. In 10%, a change of biological agent to vedolizumab was required. High doses of prednisolone at the start of treatment were associated with increased mortality, apparently due to the initially heavier condition. Improvement with infliximab was observed from the third day of treatment. Symptoms completely subsided on day 31. In 24% of the patients, hospitalization of 7 days was required. Secondary gastrointestinal infections mainly due to Clostridioides difficile occurred in 16%.[54]

Some cases of CIC do not respond adequately to vedolizumab or infliximab. There are no formulated guidelines for these patients, but small-molecule biological agents, particularly tofacitinib, have been used in individual cases. Kono *et al.* used upadacitinib, a Janus kinase inhibitor, as the recommended treatment for ulcerative colitis and Crohn's disease, with a dose of 45 mg daily. Rapid improvement in both clinical and endoscopic findings was observed. The authors of this review of data and the satisfactory results of this micromolecular agent in the treatment of IBD recommend the drug in refractory cases until prospective studies in a sufficient number of patients demonstrate the efficacy of the drug.[55]

In a recent review, Tauseef *et al.* argue that cyclosporine and mycophenolate mofetil can be used in addition to biological agents.[56] It is well known that sargramostim (glycosylated, yeast-derived, recombinant human) contributes to the homeostasis of the gastrointestinal tract and mucosal healing. It further enhances mucosal immune responses through differentiation and maturation of monocytes, macrophages, and neutrophils and induction of T-cell anti-inflammatory responses. In experimental models of colitis, growth factors were shown to help heal the condition.[57] Sargramostim was also shown to reduce the severity of Crohn's disease in patients. Interestingly, a recent observation is that the administration of sargramostim, a long-standing growth factor widely used in clinical practice in various conditions, may provide therapeutic benefits in patients with CIC without adversely affecting anticancer therapy. The drug co-administered with ipilimumab reduces severe digestive side effects compared to ipilimumab administration alone. Shortly, sargramostim may have a place in the prophylactic treatment of side effects of ICI therapy, possibly improving survival as well.[58]

In an interesting study, Ghosh *et al.* developed inflammation-targeting nanoparticles using biopolymers derived from the gum kondagogu (Cochlospermum gossypium) plant. In this way, they achieved selective, uniform, and sustained drug release into inflammatory areas of the intestine of humans and experimental animals (mice), thus improving the therapeutic effect. Furthermore, they demonstrated that oral administration of inflammation-targeting nanoparticles loaded with a microbial metabolite (urolithin A or its synthetic analog UAS03) significantly reduced the incidence of CIC in preclinical models.[59]

Besides, Ho *et al.* published the results of an accelerated management paradigm for patients with ipilimumab-induced diarrhea (> five loose stools/day) and the possible development of CIC. In these patients, treatment with ICI was interrupted, and therapy with methylprednisolone was initiated. If diarrhea was not resolved, high-dose steroids and infliximab were promptly added. Among 242 patients under treatment with ipilimumab, 46 developed significant diarrhea (19%), and 34 (74.4%) had a rapid resolution (8.5 ± 16.4 days) of diarrhea following corticosteroid and infliximab treatment. There were no intestinal complications or deaths. Immunosuppressive therapy for diarrhea did not decrease the remission rate or survival. After the control of diarrhea, most patients were able to continue their planned immunotherapy.[60]

It is known that patients with inflammatory bowel disease are predisposed to the development of malignant neoplasms not only in the intestinal tract but also in other organs outside the digestive tract. Therefore, what is the effect of the applied anticancer therapy, and especially ICIs, on the course of the underlying enteropathy in a patient who simultaneously developed a malignant neoplasm? The answer to this question is not clear. Grimsdottir *et al.*, in a recent systematic review, evaluated the effects of anticancer therapies on the activity of inflammatory enteropathy. They included 33 studies of 1298 patients with inflammatory enteropathy who received anticancer treatment. The incidence of recurrence of enteropathy after anticancer therapy was 30%. Relapses of enteropathy resulted in discontinuation of anticancer treatment in 14% of patients. The risk of gastrointestinal toxicity after therapy with ICIs was increased compared with patients without enteropathy, although the flare-ups were not of severe severity. Therefore, a notable proportion of patients with inflammatory enteropathy will experience disease recurrence during anticancer therapy. However, flare-ups are manageable and should not preclude anticancer treatment.[61]

Based on the vast experience available on the diagnosis and treatment of inflammatory bowel disease, guidelines

for the diagnosis and treatment of CIC should be formulated based on the (albeit incomplete) literature. In addition, these guidelines should include data on the efficacy of other biological agents, including micromolecular agents. Some recommendations could be made based on the current guidelines and the published data up to the end of 2024. In general, vedolizumab and infliximab should be considered as preferred biological agents, without excluding the use of other biologicals, including ustekinumab, as well as other biologics, including mainly macromolecules such as upadacitinib, and tofacitinib. The role of immunosuppressants, as well as the role of budesonide and fecal transplantation, should be further investigated. Finally, the remission of symptoms may allow the oncologist to reintroduce anticancer therapy always with the agreement of the clinical gastroenterologist.

## OUTCOMES

Most cases of CIC will not recur except in the case of continued treatment with ICIs. The decision to restart treatment with the ICI that caused the complication depends on many factors, such as the type of underlying neoplasm, the severity of the colitis, and the patient himself. Suppose it is deemed necessary to continue treatment with the same ICI. In that case, this should be done in patients who have experienced mild symptoms but should permanently discontinue treatment as soon as diarrhea or colitis recurs. Conversely, patients with severe symptoms should discontinue ICI treatment. It has been described that continuing treatment with one of the biological agents (infliximab or vedolizumab) may result in a reduction in the rate of recurrence of colitis.

Regarding the clinical outcome of patients with CIC, Lenti *et al.*, in a multicenter, retrospective, European study, described the 12-month clinical outcome of patients with CIC-induced colitis. They used the CTCAE in 96 patients suffering mainly from lung cancer and malignant melanoma. Interestingly, an inflammatory bowel disease-like pattern was present in 77.1% of the patients, while microscopic colitis was present in 19.8%. The 12-month clinical remission rate was 47.7 per 100 person-years. ICI was discontinued in 79.5% of the patients. According to the histopathology picture, the remission rate was not achieved in patients with a Crohn's disease-like pattern. At the same time, histopathological signs of microscopic colitis were associated with a better outcome. Discontinuing the ICI was not related to the 12-month remission. Three percent of the patients (3.1%) died from CIC. These results suggest that patients with Inflammatory bowel disease like CIC need an early and more aggressive treatment.[62]

## CONCLUSION

The epidemiology of diarrhea and/or colitis that can occur during treatment with ICIs of many malignant tumors is well documented. The aetiopathogenesis is still unclear, although significant advances have been made. The gut microbiota, including Faecalibacterium prausnitzii, Bacteroides fragilis, and Lactobacillus reuteri, play a critical role in developing colitis associated with ICI therapy. Endoscopy demonstrates existing inflammation and allows biopsies to be taken. Biopsy of the mucosa contributes decisively to the diagnosis. Current management is based on administering corticosteroids and, in severe cases, on administering biological agents alongside symptomatic treatment.

There is no data on the successful prevention of symptoms (diarrhea) and the occurrence of CIC. A randomized, placebo-controlled study designed to prevent the occurrence of CIC after ipilimumab use *via* topical application of budesonide failed to achieve positive results.[63] However, the use of budesonide either as a preventive treatment or as a treatment for the acute phase of colitis should be thoroughly investigated in the future.

The clinical and therapeutic data on CIC's pathogenesis, diagnosis, and treatment are generally insufficient. Prospective studies are needed on the type, duration, and effects of treatment with biological agents on colitis and the underlying neoplastic disease whose clinical behavior may be modified.

Using inflammation-targeting nanoparticles is expected to significantly enhance therapeutic efficacy by administering smaller doses of drugs with fewer side effects. This targeted approach can also be used in patients with inflammatory bowel disease, minimizing systemic side effects of treatment.

Concurrent therapy with anti-TNFα and ICI is safe, facilitates steroid tapering, and prevents CIC. However, prospective clinical trials are needed to assess the outcomes of this treatment modality.

The impact of CIC outcomes on patient survival should be further investigated.

Strategies to restore or prevent microbiome dysbiosis in the context of immunotherapy toxicities should be further explored in prospective clinical trials.

Future studies should also focus on how to improve long-term clinical outcomes.

Finally, select genetic polymorphisms (ATG16L1T300A) and serum amyloid A warrant further study as potential

biomarkers associated with severe CIC.

## DECLARATIONS

### *Author contributions*

All authors conceived the study and contributed to the final manuscript.

### *Conflicts of interest*

There is no conflict of interest among the authors.

### *Data sharing statement*

No additional data is available.

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