

Gastrointestinal injury induced by immunomodulators: A review article

Pingxin Zhang , Ren Mao, Chuhan Zhang, Yun Qiu and Minhu Chen 

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Abstract: An increasing number of immunomodulators, either anti-inflammatory or immunity-enhancing, have brought about a revolutionary effect in the management of a variety of autoimmune disorders and malignancies. However, their ability to cause gastrointestinal (GI) injury and induce GI symptoms has been increasingly and unexpectedly recognized. GI injury associated with immunomodulators may demonstrate various histologic and endoscopic patterns. Optimal diagnosis and treatment require a multidisciplinary approach. This review aims to provide an overview of the literature on its pathogenesis, the clinical, endoscopic, and histologic features, and suggested approaches to manage these newly recognized immunomodulator-induced GI adverse effects (AEs). We also reviewed current biomarkers predictive of GI toxicity and potential risk factors to identify susceptible patients. In addition, these immune-mediated AEs were compared with inflammatory bowel disease, a well-documented form of inflammation-driven GI injury. We hope this review will raise awareness and vigilance among clinicians of these entities to increase early diagnosis and rapid referral to specialist care.

Keywords: adverse effects, colitis, gastrointestinal tract injury, immunomodulators

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Introduction

Adverse drug reaction is a non-negligible tissue in clinical activities considering the increasing numbers of prescription or nonprescription drugs. As the primary place contacting with and absorbing drugs, gastrointestinal (GI) tract injury has become one of the main manifestations of adverse drug reactions. According to the Annual Food and Drug Administration report in 1995, GI events accounted for 10% of all drugs adverse effects (AEs).¹ In elder people, GI AEs are listed in the dispensatories of ~2/3 of all the marketed medicines.² Some symptoms caused by drugs are reversible and mild such as abdominal pain, nausea, vomiting, diarrhea, appetite decrease, etc., while others such as peptic ulcer, perforation, and bleeding may lead to poor prognosis or even life threatening.³ In recent years, as molecules designed to regulate the immune pathways, a variety of immunomodulators have been applied either to reduce the immune response against

transplanted organs and autoimmune diseases or to boost the immune system's capacity to attack or even eliminate cancer. In the United States, the use of immunomodulators has reached 2.7–6.2%.^{4,5} With the increasing use of immunomodulators in clinical practice, AEs targeting the GI tract should raise the awareness and vigilance among clinicians as they may cause significant morbidity and reduce patients' quality of life. Moreover, GI AEs are commonly overlooked by physicians due to their focus on primary disease status. The spectrum of GI toxicity so far is poorly defined especially for constantly developed new targeted immunomodulators which may carry potential GI toxicity.

Herein this review aims to summarize the GI injuries induced by immunomodulators from the aspect of mechanisms, clinical, endoscopic, and pathological characteristics, and recommended management.

Correspondence to:

Yun Qiu
Department of
Gastroenterology, The
First Affiliated Hospital,
Sun Yat-sen University,
No. 58 Zhongshan Road II,
Guangzhou, Guangdong
Province 510080, P.R.
China
qyun@mail2.sysu.edu.cn

Pingxin Zhang
Ren Mao
Chuhan Zhang
Minhu Chen
Department of
Gastroenterology, The
First Affiliated Hospital,
Sun Yat-sen University,
Guangzhou, Guangdong
Province, China

Mycophenolate mofetil

Mycophenolate mofetil (MMF) has been widely used in solid organ transplant recipients for the prevention of immunological rejection. MMF acts as an inhibitor of a key enzyme of inosine monophosphate dehydrogenase in the *de novo* pathway of purine synthesis which is essential for the proliferation and function of lymphocytes thus causing lymphocyte-selective immunosuppression.⁶

Although the AE profiles of MMF are comparatively benign, GI AEs are still a major concern which may partially be explained by the increased immune suppression and interactions with other immunosuppressants. Mucosal dysfunction due to inhibition of epithelial cell growth and local lymphocyte depletion may render mucosa susceptible to infection.⁷⁻¹⁰ Other pathogenesis factors include dysregulation of intestinal microecology.¹¹

GI AEs, including nausea, vomiting, diarrhea, and abdominal pain, appeared in up to 45% of patients receiving MMF.^{7,9} Diarrhea is the most frequent AE observed in renal transplant recipients.⁷ Other complications such as intestinal perforations and GI hemorrhage are rare but pose major concerns.

The endoscopy reveals a variety of patterns of colonic mucosal injury, including non-specific colitis (31.3%), inflammatory bowel disease (IBD)-like colitis (25.0%), normal/near-normal findings (18.8%), graft-*versus*-host disease (GVHD) like (18.8%) and ischemia-like colitis (12.5%).¹²

MMF-associated colitis is histologically characterized by crypt distortion, prominent crypt cell apoptosis, edematous lamina propria, and inflammatory cells infiltration, which are similar to IBD (Supplemental Table 1) and GVHD.^{13,14} Even some case reports provided evidence of celiac-like duodenopathy as a rare complication of MMF in kidney transplant recipients. These patients who were negative in serology and HLA genotyping for celiac disease presented with severe chronic diarrhea and substantial weight loss. The major histology pattern from duodenal biopsies showed a combination of villous atrophy and intraepithelial lymphocytosis, and lack of epithelial cell apoptosis and prominent lymphoplasmacytic mucosa infiltrates, which differed from genuine celiac disease.¹³

Most GI AEs caused by MMF are self-limiting. A prospective study showed that switching to enteric-coated MMF had a significant improvement in GI-related toxicities in liver transplant recipients.¹⁵ Splitting the dose, reducing the dosage by 50%, or reducing or discontinuing combined medication can be effective if the symptoms are mild. Moderate symptoms such as serious nausea, vomiting, anorexia, abdominal pain, and body weight loss persist for more than 10 days, MMF withdrawal is recommended if the above measures do not work or in case of GI ulcers or ischemic colitis.⁷

Immune checkpoint inhibitors

Immune checkpoints are the correction points of the body's immune response, and the existence of these inhibitory pathways is crucial for maintaining self-tolerance and regulating immune responses in peripheral tissues. The normal function of the immune checkpoint can minimize tissue damage when immune responses are activated. Many tumor cells can avoid being killed by negatively regulating the immune system, and immune checkpoints are one of the targets.¹⁶ Immune checkpoint inhibitors (ICIs) are a group of monoclonal antibodies including anti-cytotoxic T-lymphocyte associated protein-4 (CTLA-4), anti-programmed death-1 (PD-1), or anti-PD1 ligand 1 (PD-L1) molecules. ICIs have been approved as effective treatments for a wide range of malignancies, such as melanoma and non-small-cell lung cancer (NSCLC).^{17,18}

GI injuries associated with ICIs use are diverse which included enterocolitis, GI perforation, megacolon, intestinal obstruction, diarrhea, IBD-like, GI hemorrhage, abdominal discomfort, and vomiting.¹⁹ The most frequent GI event is enterocolitis, with an incidence of 21% of patients on ipilimumab.²⁰ The incidence of diarrhea was ranged from 30.2% to 35.4% with anti-CTLA-4 therapy as compared to 12.1–13.7% that of anti-PD-1 users according to a systematic review.²¹ Other rare GI toxicities include bowel perforation (<1%) and pancreatitis (<1.5%).²²

Immune-mediated diarrhea and colitis (IMDC) is among the most common immune-related AEs in patients with ICIs. Predictors for risk of IMDC included the type of ICI used, underlying cancer, and patients' characteristics. A

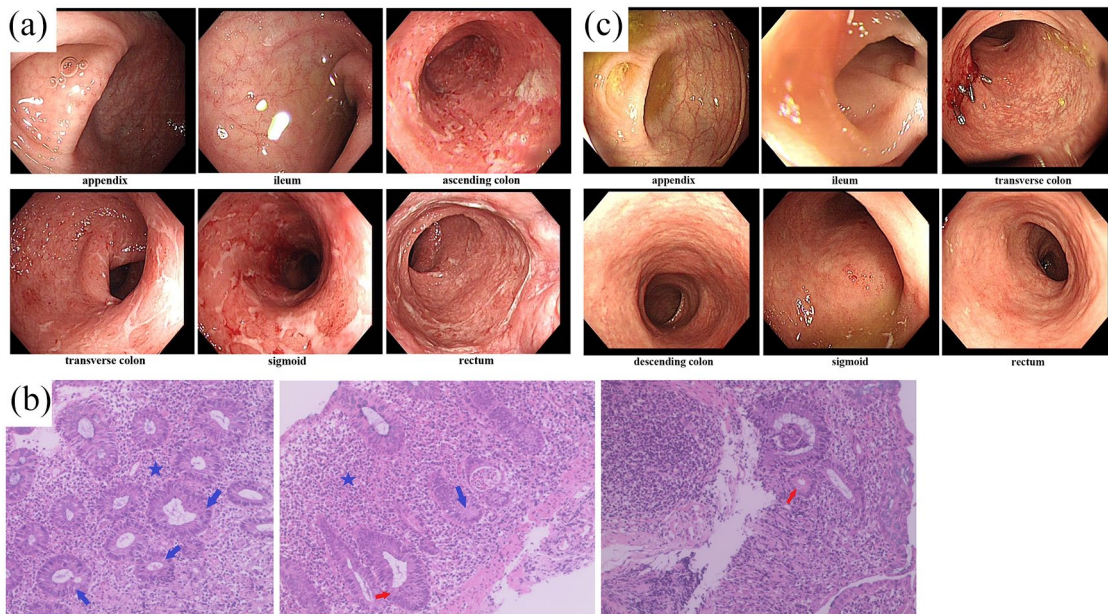


Figure 1. Sinitilimab-induced colitis were successfully treated with infliximab. Male, 36 years, complained of bloody diarrhea for 4 months, and received nine injections of Sinitilimab for a malignant mesenchymal tumor of the right shoulder. (a) The mucosa of the whole colon was friability with loss of normal vascular pattern, covered with a large number of irregular ulcers and spontaneous bleeding. (b) Biopsy revealed severe active chronic inflammation, crypt abscess, and deformed crypt branches. More importantly, scattered apoptotic bodies (arrow indicated) can be seen. After a full screening of possible infectious etiology, a diagnosis of IMDC (grade 4) was made. Sinitilimab was discontinued permanently and infliximab (5 mg/kg) was given immediately. The patient's symptoms resolved rapidly with a gain of weight. (c) Mucosal healing was achieved after three injections of infliximab.

recent study showed that preexisting IBD significantly increased the risk of IMDC.²³ This multicenter, retrospective study included 102 patients with documented IBD who received ICIs therapy, GI AEs occurred in 42 patients (41%), a rate higher than in patients without underlying IBD (11%, $p < 0.001$). Among the GI events in patients with IBD, 21 patients (21%) had grade >3 diarrhea, 4 patients experienced colonic perforation, and 2 of whom required surgery.²³

Endoscopic features of GI injuries associated with ICIs include erythema, erosions, bleeding, and mucosal edema (Figure 1(a)). Within the small bowel, features resembling celiac disease can be observed, including scalloping of folds and a reduction in fold number,^{24,25} and loss of vascular pattern.²⁶

Histologic characteristics of ICIs induced GI injuries include expansion of lamina propria with mixed inflammatory infiltrates, focal cryptitis, crypt abscesses, rare apoptotic epithelial cells,

and focal clustering of histiocytes centered on damaged glands.²⁶ Ruptured granuloma can be seen in some cases.²⁷ There are two major patterns of anti-PD-1-associated colitis, an active colitis pattern with increased apoptosis and crypt atrophy (Figure 1(b)) and a lymphocytic colitis pattern.

Several cohort studies have outlined the similarities and differences between ICI colitis and IBD.²⁸ Clinically and endoscopically, there is a high overlap, including the negative prognostic significance of deep ulceration. Histologically, ICI colitis may present as either acute colitis or demonstrate features of chronic damage, including IBD-like and lymphocytic colitis-like phenotypes. Current treatments for ICI colitis are based on steroids and infliximab, which are also standard therapy to induce remission of IBD flares. Overall, ICI colitis represents a distinct form of colitis with characteristics resembled of IBD flares. A comprehensive characteristics comparison between ICI colitis and IBD is detailed in Supplemental Table 2.

The precise mechanism of IMDC has not been elucidated, which may be related to the inhibition of relevant immune pathways, and the imbalance of intestinal microecology. The attack of normal tissue by both activated T cells and hyper-enhanced inflammation may be potential mechanisms.²⁹ Positive interaction of intestinal dendritic cells and circulating T cells by specific taxonomic groups of intestinal bacteria may play a role.³⁰ Several cohort studies have associated the gut microbiome with response to ICIs.^{31,32} Two interventional studies in advanced melanoma have demonstrated that fecal microbiota transplant (FMT) can convert non-responder to become responders to anti-PD1 immunotherapy.^{33,34} Furthermore, ICI-triggered toxicities are also associated with patients' microbiome³¹ and there is a potential role for FMT to ameliorate toxicities.³⁵ As a large-scale, multi-center study involving up to 40 United Kingdom sites, the MITRE trial will generate the largest cancer microbiome dataset according to their recently published protocol,³⁶ which aimed to prospectively evaluate and validate a gut microbiome 'signature' to predict the efficacy and toxicity in cancer patients receiving ICI therapy.

Early recognition, evaluation, and appropriate management are crucial to ensure an optimal outcome and minimize treatment interruption of patients on ICIs. Prompt endoscopy evaluation is associated with a better outcome and should be used to assess disease severity and guide management.³⁷⁻³⁹ For most patients, symptomatic treatments such as fiber, probiotics, and loperamide are effective. Corticosteroids remain to be the cornerstone in managing IMDC. In refractory cases, biologics including infliximab (Figure 1(c)) and vedolizumab both are reasonable options in moderate- to high-risk or steroid-refractory low-risk patients. When steroids failed in moderate-to-severe diarrhea, termination of ICIs should be considered.⁴⁰ For severe (grade >3) toxicity, when peritoneal signs indicate bowel perforation or obstruction, ICIs should be permanently discontinued. Surgery is preferred in case medication intervention failed.^{17,18,26,41} Recently, FMT was shown to promote a response in ICI refractory melanoma patients.³⁴ Outcomes from the MITRE study can be expected which may guide future strategies by manipulating patients' microbiomes to enhance treatment efficacy and to develop co-therapies to increase the efficacy of ICIs.³¹

Phosphoinositide-3 kinase inhibitors

The signaling pathway mediated by phosphoinositide-3 kinase (PI-3K) exerts pleiotropic effects on cell metabolism, migration, proliferation, survival, and differentiation.⁴² Idelalisib, as the first-in-class selective inhibitor of δ isoform of PI-3K, has been proven for the treatment of several indolent B-cell malignancies by impeding B-cell proliferation, chemotaxis, adhesion, and promoting its apoptosis.^{43,44}

However, immune dysregulation including decreased number and activity of regulatory T cells (Treg), and enhanced cytotoxic T cells may occur following the inhibition of PI-3K pathway which may partly explain the GI damage caused by idelalisib.⁴⁵⁻⁴⁷ In addition, infection followed by dysfunction of toll-like receptor pathway and hinder of Treg recruitment may be another cause of idelalisib-induced GI injury.^{44,48} Ibrutinib, as the first-in-class inhibitor of Bruton tyrosine kinase, plays a similar role in inhibiting the signal transduction in B-cell surface; nonetheless, the safety profile of ibrutinib is distinct from that of idelalisib.^{49,50} During ibrutinib treatment, bleeding and atrial fibrillation can pose especially complex treatment dilemmas, whereas diarrhea, pneumonitis, and abnormal liver function are challenging in idelalisib treatment.

In a retrospective analysis of nine clinical trials, 15% of patients on idelalisib developed grade 3-4 diarrhea and/or colitis.^{24,44} The rate of any grade of diarrhea even reached 47% among 146 patients with indolent non-Hodgkin lymphoma on 150 mg idelalisib monotherapy.⁴² Other GI events include dyspepsia, abdominal pain, worsening colitis, hematochezia, and bowel perforation.

The endoscopic manifestations have not been fully reported. Colitis, diverticulitis, and colonic wall thickening can be seen in some cases on idelalisib use.⁴⁴

The histological features can be summarized into four types: apoptosis pattern, glands atrophy pattern, glands atrophy within the background of inflammation, and normal pattern. Typically, intraepithelial lymphocytosis, epithelial cell apoptosis, and neutrophilic cryptitis can be observed in the involved bowel segments.^{27,44}

GI events, especially diarrhea, is one of the prominent symptoms in most patients,⁴² which can be

divided into two types: spontaneous and idelalisib related. The first type generally occurs within the first 8 weeks and is typically mild or moderate (grade 1–2) and responsive to common antidiarrheal agents (e.g. loperamide). The second type occurs relatively late and responds poorly to antidiarrheal or empiric antimicrobial therapy. In late-onset idelalisib-related diarrhea (grade 2–3), budesonide, and oral or intravenous steroid are recommended. If life-threatening diarrhea (grade 4) occurs, idelalisib should be permanently discontinued.⁵¹

EGFR inhibitors

Epidermal growth factor (EGF) is one of the cytokines promoting cell growth through the combination with EGF receptor (EGFR). Tumor cell motility, adhesion, and metastasis have all been found to be facilitated by the overexpression of EGFR.⁵² As specific antibodies against EGFR, cetuximab and panitumumab selectively targeting tumor cells and inhibiting their growth and spread, are increasingly used in NSCLC, colon cancer, and other carcinomas.^{24,53}

The exact mechanism of GI AEs caused by anti-EGFR has not been elucidated. Once the autophosphorylation and activation of EGFR of GI epithelial cells have been blocked, several downstream signaling pathways including JAK-STATs, RAS-PI-3K, RAS-Raf, and PLC γ -PIP2 which are essential in protein synthesis, cell growth, cell regeneration, and motility are inactivated⁵⁴ which may lead to GI damages.

Anti-EGFR-related GI toxicities including diarrhea, nausea, and vomiting are not rare. For panitumumab, the incidence of all grades of diarrhea is 21% and the incidence of grade 3–4 diarrhea is 2%. Nausea was observed in 64% of patients treated with cetuximab and 23% of patients with panitumumab, and vomiting occurred in 19% of patients (2% grade 3–4).⁵⁵ As demonstrated in a meta-analysis of 18 clinical trials with anti-EGFR therapy, the incidences of severe diarrhea (grade 3–4) and mucositis/stomatitis were 18% and 8% (compared with the control arm of 11% and 2%), respectively.⁵⁶ Some cases reported other rare GI symptoms, including pneumatosis intestinalis and ileal perforation^{57–60} and GI hemorrhage⁶¹ with endoscopic evidence of severe mucosa congestion and erosion.

The therapy for anti-EGFR-related diarrhea includes bowel rest, hydration, replacement of

electrolytes, and loperamide or diphenoxylate. In case, symptoms worsened, hospitalization should be considered.⁶²

Tyrosine kinase inhibitors

As an enzyme, protein tyrosine kinase (PTK) catalyzes the transfer of ATP- γ -phosphate to the tyrosine residue of the protein and makes it phosphorylation, which plays a vital role in the regulation of cell growth, differentiation, and death.⁶³ Tyrosine kinase inhibitors (TKIs) can selectively inhibit cancer cell proliferation by binding to the ATP catalytic site of the corresponding PTK.⁶⁴ For now, several TKIs have been approved for the treatment of metastatic NSCLC, colorectal cancer, squamous-cell carcinoma of the head and neck, and pancreatic cancer.^{65,66} There are similarities and specificities considering the mode of action of different TKIs (Supplemental Table 3).

The ubiquitous expression of the EGFR on the cellular surface of the GI epithelial tract may lead to a high incidence of diarrhea.⁵⁵ The excessive chloride secretion in the GI tract due to negative regulation by ErbB receptors is one of the potential mechanisms in TKI-induced diarrhea.^{67–69}

Different TKIs exhibit similar GI toxicity including diarrhea, nausea, and vomiting with differed incidences. The incidence of diarrhea and vomiting can reach 90% and 20% in the patients treated with Afatinib. About 30–54% of patients developed nausea when receiving Sunitinib. Some rare GI side effects have been reported including intestinal hemorrhage and colitis,^{70,71} duodenal perforation,⁷² and ileal perforation.⁷³

Grade 1–2 diarrhea can be handled with loperamide. In case, loperamide does not work, reduction in TKIs instead of discontinuation is reliable management. Discontinuation of TKIs should be considered when grade 3–4 diarrhea occurs. TKIs can be restarted when a patient returned to normal bowel habits or in case of grade <1 toxicity.^{74–77}

HER-2 inhibitors

HER-2, as a member of the ErbB family, and its receptor are associated with multiple signal pathways which regulate cell proliferation, cell survival, cell motility, and angiogenesis.^{78,79} Pertuzumab, together with trastuzumab, is a

monoclonal antibody that binds to HER-2 at extracellular subdomain II and impedes ligand-dependent dimerization with other HER receptors, including EGFR, HER-3, and HER-4. This monoclonal antibody is mainly prescribed as a basic therapy for some HER-2-positive cancer, such as breast cancer and gastric cancer.⁸⁰

GI events related to HER-2 antibodies may be associated with the blockage of normal metabolic activities of cells in the GI tract. Other mechanisms that cause diarrhea involved altered gut motility, colonic crypt damage, and dysbiosis which leads to altered fluid transport and absorption in the colon.⁸¹

According to a phase I trial, pertuzumab-induced AEs included vomiting (52%), nausea (48%), abdominal pain (48%), and diarrhea (43%). One patient developed GI bleeding which was graded as level 3 dose-limiting toxicity.⁸² Trastuzumab-induced GI toxicities were observed in 12% of administrators, and symptoms included nausea, vomiting, diarrhea, abdominal pain, and bloating.⁸³ The incidence of all-grade diarrhea across studies was generally higher for pertuzumab-based treatment, and also more often in Asian or elderly patients, which ranged from 28% to 72%.⁸⁴

Drug withdrawal due to GI toxicities is rare. When diarrhea or vomiting occurs, symptomatic treatment including loperamide or antiemetics is considered.⁷⁴ In severe refractory diarrhea, rifaximin might be a choice.⁸⁵

VEGF inhibitors

Angiogenesis contributes to the progression, invasion, and metastasis of malignancy and anti-angiogenesis plays a vital role in the treatment of tumors.⁸⁶ Vascular endothelial growth factor (VEGF) can activate several cellular processes, including angiogenesis, vascular permeability, vascular survival, and lymphangiogenesis.^{87,88} The monoclonal antibodies, such as bevacizumab, can bind to and neutralize VEGF and bioactive proteolytic fragments.⁸⁹ Since bevacizumab was first approved by the FDA in 2011, several anti-VEGF agents have been introduced for the treatment of NSCLC, renal cell cancer, ovarian cancer, and glioblastoma multiforme.⁹⁰

Bevacizumab-induced local ischemia due to inadequate vascular perfusion of GI tissue and compromised vascular integrity resulting from a disturbance in endothelial cell and platelet interaction were potential pathophysiologic mechanisms leading to GI perforation.^{88,91}

GI symptoms include nausea, vomiting, anorexia, gastritis, and diarrhea have been reported in clinical trials.⁹² The incidence of diarrhea significantly increased in patients treated with angiogenesis inhibitors (risk ratio 1.66, 95% CI: 1.11–2.50; $p=0.01$).⁹³ GI perforation is another well-documented and fatal toxicity for patients receiving anti-VEGF.⁹⁰ In a large observational cohort study (Bevacizumab Regimens: Investigation of Treatment Effects and Safety), 1.8% of patients who received bevacizumab developed GI perforation.⁹⁴ The result was further confirmed by Fairouz *et al.*, 37 (1.9%) experienced GI perforation when receiving bevacizumab combination chemotherapy.⁹¹ In a meta-analysis, a significantly increased risk of GI perforation was observed in bevacizumab-containing therapy (risk ratio 3.08, 95% CI: 1.04–9.08; $p=0.042$).⁹⁵ GI ulcer, perforation, or perforated ulcer was more likely to be observed in the combination of chemotherapy and bevacizumab. The histology specimens exhibit ulceration or/and granulation tissue with neovascularization.⁹⁶

Management of diarrhea induced by anti-VEGF is similar to other immunomodulators. Mild diarrhea can be handled by loperamide, oral hydration, and electrolyte replacement. Oral diphenoxylate, atropine, or budesonide can be considered in grade 2 diarrhea. Grade 3/4 diarrhea should be treated with intravenous steroids. If the GI symptoms persist, immunomodulators (cyclophosphamide or MMF) can be considered.^{97,98} Surgery is indicated in the case of GI perforation. Nonoperative management including placement of a percutaneous intra-abdominal catheter, intravenous injection antibiotics, and bowel rest has also been proven to be succeeded in some cases.⁹⁹

Anti-CD20 monoclonal antibody

Rituximab, a murine-based immunoglobulin G1 monoclonal antibody targeting CD20 antigen, has been approved for the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, and

follicular lymphoma.¹⁰⁰ Now it is also used in the management of nephrotic syndrome.¹⁰¹

B cells in gut-associated lymphoid tissue were shown to protect against autoimmune disease through the promotion of transforming growth factor beta and interleukin 4 in mice.¹⁰² Anti-CD20 antibodies systematically deplete B cells, including those located in the GI tract, resulting in the decreased effect of B cells both in the negative regulation of CD4+ T-cell activity and the removal of apoptotic cells from the mucosa. In addition, the depletion of B cells may lead to Treg dysfunction with subsequent stimulation of auto-reactive cytotoxic T cells in GI tissues.^{103,104} This disequilibrium of the immune system in the GI tract plays an important role in the pathogenesis of intestinal inflammatory injury which may cause severe colitis in susceptible rituximab patients.

As the most common rituximab-induced GI AEs, the clinical features of colitis included diarrhea, abdominal pain, bloody stool, and vomiting. More severe AEs such as colonic perforation and rituximab-related IBD had been reported.^{100,105–107}

According to a recent study, pan-colonic inflammation (58%) was the most common endoscopic feature, and its pattern included nonulcerative inflammation (21%) or ulcers (13%).¹⁰⁰ The histologic features of rituximab-induced colitis included an increase in lymphocytes and granulocytes in the lamina propria, erosion, ulceration, and apoptotic bodies.¹⁰⁰

There is no consensus for the treatment of rituximab-induced colitis for now. Antibiotics and intravenous fluids were suggested to control the clinical symptoms. For patients who developed colitis-related perforation, hemicolectomy may be required.¹⁰⁰

Calcineurin inhibitors

Calcineurin, as a key phosphatase, plays an indispensable role in stimulating the proliferation and differentiation of T cells. Calcineurin inhibitors (CNIs) are widely applied in immune-related diseases and immunosuppression after solid organ transplantation due to the inhibitory effect on T-cell activation.¹⁰⁸ There are two CNIs used in clinical

practice, including cyclosporine A (CsA) and tacrolimus (TAC). Voclosporin is another new CNI approved for the treatment of lupus nephritis.¹⁰⁹

For the rheumatoid arthritis patients receiving TAC therapy, GI symptoms (19/42, 45.2%) including nausea and vomiting, abdominal pain, diarrhea, anorexia and abdominal distension were the most common AEs.¹⁶ The incidence of diarrhea caused by TAC and CsA was up to 43–72% and 40–47%, respectively.²⁴

The mechanism of diarrhea with CNIs has not been fully clarified. Infection, drug interaction, and direct effect on the GI mucosa have been implied by previous studies.^{24,110} Moreover, the macrolide structure of TAC mimicking the action of motilin may partly explain the higher incidence of diarrhea.^{16,111}

In a group of patients receiving TAC therapy, colonoscopy examination showed erythema and/or mucosal congestion in 11 patients (55%), and erosions and/or ulcers in 3 patients (15%). The histologic findings showed that most (90%) cases present crypt epithelial regeneration with mucin depletion and variable degrees of inflammation. Unlike colitis induced by MMF, more than half of the cases on CNIs developed active colitis which is accompanied by plasma cell-rich lamina propria inflammation and crypt distortion. However, extensive necrotic epithelial cells only presented in 10% of cases.¹¹²

When GI symptoms occurred in patients on CNIs, infections should be first ruled out.¹¹⁰ Most cases of diarrhea were mild, self-limited, or only required dose reduction.¹¹³ When the GI symptoms become chronic, reduction in the CNIs or switching to other immunomodulators is suggested.¹¹²

Perspective

The damage induced by the abovementioned immunomodulators may occur in any GI segment and exhibit various clinical features. As a marker of GI injury, fecal calprotectin has been regarded as a specific predictor of intestinal inflammatory activity, especially for monitoring disease activity in IBD.¹¹⁴ Some other preclinical biomarkers for GI damage have also been

proposed, including gastrin, eosinophilic cationic protein, diamine oxidase, and bile acids. However, most of these biomarkers lack specificity, sensitivity, or technical validity, which greatly limits their clinical application.¹¹⁵ Thus, it is vitally important to find specific biomarkers for early diagnosis of GI toxicity of the ever-growing use of immunomodulators in the future. Until now, a limited number of studies have focused on the predictive factors for GI toxicity. There is an urgent need to identify susceptible patients to avoid suspected drug use.

Furthermore, the specific pathogenesis mechanism of GI injury induced by each immunomodulator still has not been fully illustrated. Possible mechanisms involved with the abovementioned immunomodulators are summarized in Figure 2, which may be largely divided into two types: autoimmune-related and non-autoimmune-related. Further clarification of the mechanisms involved in their pathogenesis will greatly enhance our

understanding and therapeutic management of these immunomodulator-mediated AEs. Moreover, how to enhance drug efficacy while avoiding potential toxicity is still challenging. Outcomes from the MITRE study can be expected to guide future strategies by manipulating patients' microbiomes to enhance the efficacy of immunomodulators.³⁶

Conclusion

This article mainly focused on GI toxicity induced by newly recognized immunomodulators. GI injury associated with immunomodulators may demonstrate various clinical, endoscopic, and histologic features. When GI events occur, clinicians should always be vigilant about whether they are associated with the immunomodulators currently in use. Specific biomarkers and potential predictive factors to identify susceptible patients developing GI toxicity are still lacking. Suggested approaches to manage these GI AEs are summarized in Figure 3. (Table 1)

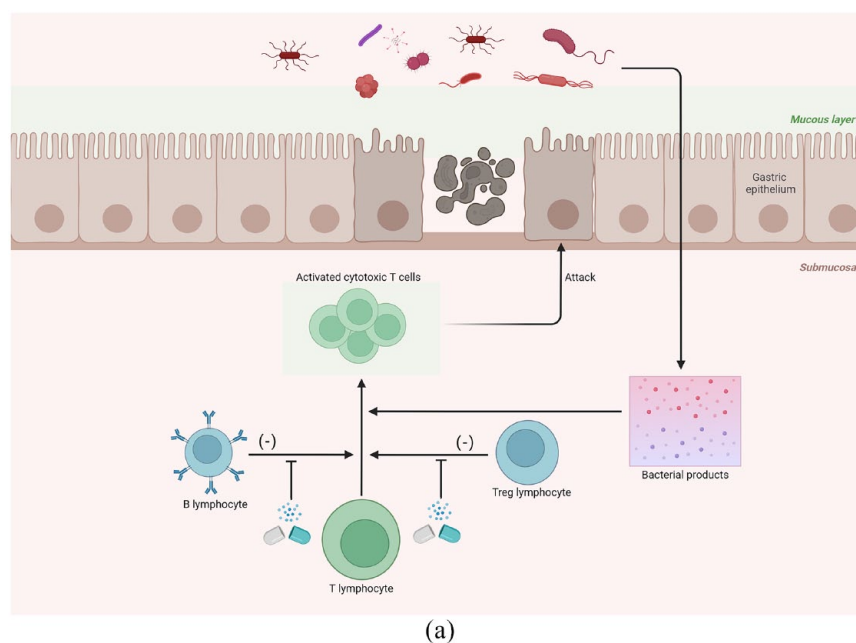
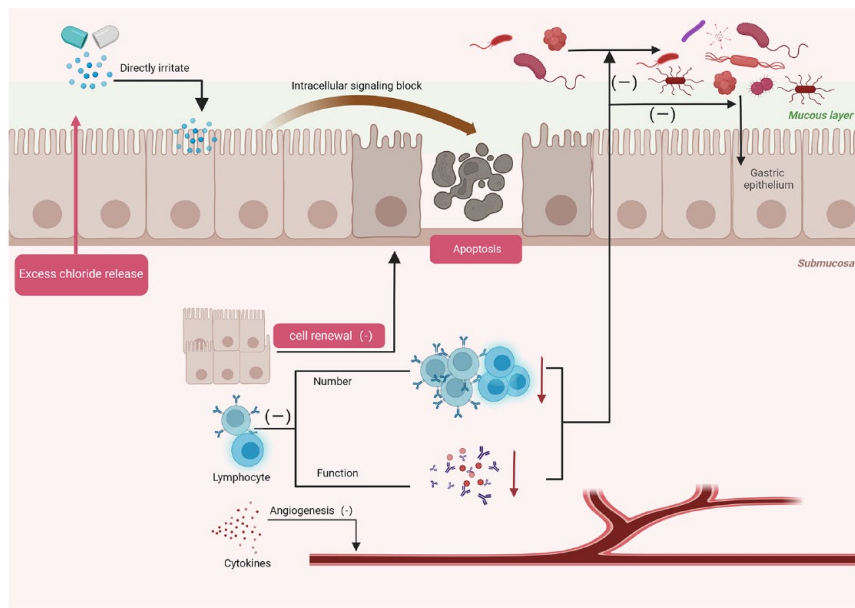


Figure 2. (Continued)



(b)

Figure 2. Mechanisms of GI injury induced by targeted immunomodulators. (a) Autoimmune related. (b) Non-autoimmune related. GI, gastrointestinal.

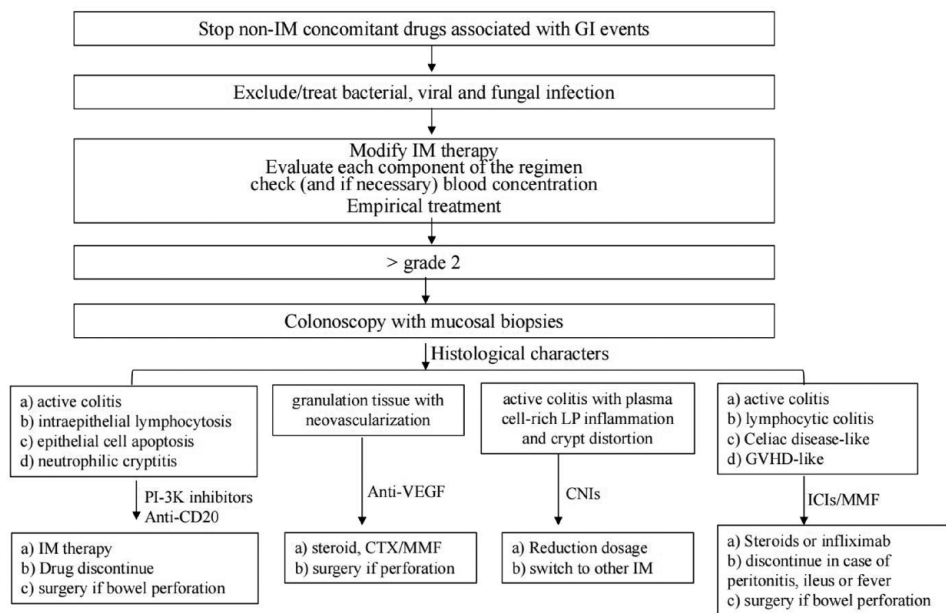


Figure 3. Suggested approach to treat GI adverse events induced by targeted immunomodulators. GI, gastrointestinal; IM, immunomodulators; LP, lamina propria.

Table 1. Summary of immunomodulator-related GI injury by its targets.

Targets	Typical drugs	Mechanism	Clinical features	Grade of small bowel injury	Endoscopic features	Histologic features	Predictors	Measures
Inhibitor of purine synthesis	MMF	(a) Inhibition of epithelial cell growth (b) Dysregulation of intestinal microecology (c) Increased immune suppression	(a) Diarrhea (most frequent) (b) Nausea (c) Vomiting (d) Abdominal pain (e) Intestinal perforations (f) GI hemorrhage	I–IV	(a) Normal/near-normal colitis (b) Non-specific IBD-like (c) GVHD-like (d) Ischemia-like colitis	(a) Crypt distortion (b) Prominent crypt cell apoptosis (c) LP inflammatory cells infiltration	NA	(a) Switch to enteric-coated MMF (b) Reduce dosage (c) Reduce or discontinue combined medication (d) Discontinue MMF in cases of ulcer diseases
CTLA-4/PD-1 inhibitors	Ipilimumab	(a) A predominance of mucosal Th1/Th17 effector responses (b) Dysregulation of gut microflora	(a) Abdominal discomfort (b) Diarrhea (c) Vomiting (d) GI hemorrhage (e) GI perforation (f) Intestinal obstruction (g) IBD like (h) Megacolon	I–IV	(a) Mucosal edema (b) Erythema (c) Erosions (d) Bleeding	(a) Active colitis (b) Lymphocytic colitis pattern (c) <i>Celiac disease-like</i> (d) GVHD-like	(a) Anti-CTLA-4 (b) Colon involvement (c) Time from IBD diagnosis to immunotherapy (d) Prior IBD surgery	(a) Drugs: fiber, probiotics, loperamide, steroids, infliximab (b) Discontinue CPIs if peritonitis occurs due to perforation, ileus, or fever (c) Surgery if bowel perforation occurs
PI-3K inhibitors	Idelalisib, ibrutinib	(a) Immune dysregulation: decreased number and activity of Treg, and enhanced cytotoxic T cells (b) Infection followed by dysfunction of TLR pathway	(a) Diarrhea (most frequent) (b) Dyspepsia (c) Abdominal pain (d) Worsening colitis (e) Hematochezia (f) Bowel perforation	NA	Colitis diverticulitis	(a) Intraepithelial lymphocytosis (b) Epithelial cell apoptosis (c) Neutrophilic cryptitis	NA	(a) Loperamide (b) Oral or intravenous steroid (c) Discontinue if grade 4 diarrhea occurs
Anti-EGFR antibodies	Cetuximab, panitumumab	Several downstream signaling pathways are blocked	(a) Diarrhea (most frequent) (b) Nausea (c) Vomiting (d) Pneumatosis intestinalis (e) Ileal perforation (f) GI hemorrhage	I–IV	Mucosa congestive and erosive	NA	NA	Loperamide, diphenoxylate

(Continued)

Table 1. (Continued)

Targets	Typical drugs	Mechanism	Clinical features	Grade of small bowel injury	Endoscopic features	Histologic features	Predictors	Measures
Tyrosine kinase inhibitors (TKI)	Afatimib	(a) Mucosal atrophy (b) Block of epithelial restitution	(a) Diarrhea (most frequent) (b) Nausea (c) Vomiting (d) Intestinal hemorrhage (e) Colitis (f) Duodenal perforation (g) Ileal perforation	I–IV	Most large bowel covered with blood	NA	NA	(a) Loperamide dosage reduction (b)
HER-2 inhibitors	Pertuzumab	(a) Blockage normal metabolic activities of GI cells (b) Altered gut motility (c) Colonic crypt damage (d) Dysbiosis	(a) Vomiting (b) Nausea (c) Abdominal pain (d) Diarrhea (e) GI bleeding	III–IV	NA	NA	NA	Loperamide, rifaximin
VEGF inhibitors	Bevacizumab	(a) Local ischemia due to inadequate vascular perfusion of GI tissue (b) Compromised vascular integrity resulting from a disturbance in endothelial cell and platelet interaction	(a) Nausea (b) Vomiting (c) Anorexia (d) Gastritis (e) Diarrhea (f) GI perforation	III–IV	Ulcer or perforated ulcer	(a) Ulceration (b) Tissue with neovascularization	(a) History of treatment for IBD (b) Bowel resection at primary surgery (c) Intact primary tumor and prior adjuvant radiotherapy*	(a) Drugs: loperamide, diphenoxylate, oral or iv. Steroid, CTX/MMF (b) Intra-abdominal catheter (c) Surgery if perforation occurs
Anti-CD20 antibodies	Rituximab	The disequilibrium of the innate immune system of the GI tract may lead to the activation of cytotoxic T cells and colitis in susceptible RTX patients	(a) Diarrhea (b) Abdominal pain (c) Rectum bleeding (d) Vomiting (e) Colonic perforation (f) IBD	I–IV	Non-ulcerative inflammation, Ulcers	(a) Increase in lymphocytes and granulocytes (b) Erosion (c) Ulceration (d) Apoptotic bodies	See Supplemental Table 4	(a) IM therapy (b) Discontinue antibodies (c) Surgery if perforation occurs
Calcineurin inhibitors	CsA tacrolimus	(a) Infection, (b) Drug combination, (c) A direct effect of drugs on the GI mucosa or (d) An effect on intestinal motilin receptors	(a) Diarrhea (most frequent) (b) Vomiting (c) Nausea (d) Abdominal pain (e) Anorexia (f) Abdominal distension	I–II	(a) Erythema (b) Mucosal congestion (c) Erosions (d) Ulcers	Crypt epithelial inflammation and regeneration	Patients a) with complication or b) comorbidity c) renal impairment	(a) Reduce dosage (b) Switch to other drugs

*Intact primary tumor and prior adjuvant radiotherapy were significantly associated with increased risk of GI perforation within 6 months after starting bevacizumab. CsA, Cyclosporine A; CTX, cyclophosphamide; GI, gastrointestinal tract; GVHD, graft versus host disease; IBD, inflammatory bowel disease; IM, immunosuppressive; iv, intravenous; LP, lamina propria; MMF, mycophenolate mofetil; NA, no available data; TGF-β, transforming growth factor beta; Treg, regulatory T cells; TLR, toll-like receptor.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Author contribution(s)

Pingxin Zhang: Writing – original draft.

Ren Mao: Writing – review & editing.

Chuhan Zhang: Writing – review & editing.

Yun Qiu: Conceptualization; Supervision;
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Minhu Chen: Supervision.

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ORCID iDs

Pingxin Zhang  <https://orcid.org/0000-0002-9064-9174>

Minhu Chen  <https://orcid.org/0000-0001-8181-0846>

Supplemental material

Supplemental material for this article is available online.

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