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**Checkpoint inhibitors: What gastroenterologists need to know**

Ahmed M. Gastrointestinal, hepatic and pancreatic side effects and management

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**Abstract**

Checkpoint inhibitors are increasingly being used in clinical practice. They can cause various gastrointestinal, hepatic and pancreatic side effects. As these side effects can be serious, appropriate management is essential. The different checkpoint inhibitors with their mechanisms of actions and indications as well as evaluation and management of gastrointestinal, hepatic and pancreatic side effects are discussed in this article.

**Key words:** Checkpoint inhibitors; Immunotherapy; Management gastrointestinal; Hepatic and pancreatic side effects of checkpoint inhibitors

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**Core tip:** Checkpoint inhibitors are a kind of immunotherapy used in the treatment of various malignancies. But they carry the risk of developing different immune related side effects. Physicians should be vigilant in recognizing and appropriately managing these side effects for a better outcome.

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**INTRODUCTION**

Checkpoint inhibitors have emerged as one of the most promising modalities of anti-cancer therapy[1]. They are monoclonal antibodies which block the checkpoint proteins either on T cells or cancer cells to enhance immune response against tumor cells[2]. Normally, when our body recognizes cancer cells or foreign body, our innate immunity (macrophage, dendritic cells, natural killer cells, mast cells, neutrophils, eosinophils and basophils) tries to eliminate them. Then our adaptive immunity (B lymphocytes and T lymphocytes) starts working *via* antigen presenting cells. Checkpoint molecules are proteins that control specific cellular processes to prevent errors. Some immune checkpoint proteins help the T cells to remain active particularly in case of infection whereas other immune checkpoint proteins regulate the immune system negatively by directing the T cells to switch off. Some cancer cells synthesize high levels of such immune checkpoint proteins which can switch off the T cells and as a result, the T cells can neither recognize nor kill the cancer cells.

Some of the common checkpoint proteins include[1] cytotoxic T-lymphocyte-associate antigen 4 (CTLA-4) receptors on CD4 and CD8 T lymphocytes[2], programmed cell death protein 1 (PD-1) receptors on the surface of T cells, B cells, NK cells, monocytes and dendritic cells and[3] programmed cell death protein ligand 1 (PD-L1) or programmed cell death protein ligand 2 (PD-L2) on healthy tissues, hematopoietic cells and tumor cells.

When interaction between the PD-1 receptors and the PD-L1 (also known as B7-H1) or PD-L2 (also known as B7-H2) occurs, it promotes exhaustion of peripheral T effector cells, conversion of T effector cells to T regulatory cells (Treg cells) and inhibition of apoptosis of tumor cells[3]. Some cancer cells are able to produce PD-L1 and PD-L2 on their surface to prevent any immunological attack.

CTLA-4 becomes activated by binding to B7-1 (also known as CD80] and B7-2 (also known as CD86) on antigen presenting cells (APC) and then inhibits T-cell activation at a proximal step in the immune response. On the other hand, PD-1 limits effector T cell function by linking with PD-L1 or PD-L2 in the later stages of immune response. In the process of carcinogenesis, these immunosuppressive molecules are overexpressed[4]. Checkpoint inhibitors are monoclonal antibodies against PD-1, PD-L1 or CTLA-4 proteins. They act as a form of immunotherapy by blocking the immunosuppressive molecules that inhibit the immune system from attacking the cancer cells and as a consequence, there is an immunological boost against cancer cells[5]. As they target T cells instead of cancer cells, they can be used in various malignancies[6]. Combination of checkpoint inhibitors may give better anti-tumor response. There was 23% response rate for metastatic non-small cell lung cancer after administration of durvalumab and tremelimumab[7].

Few checkpoint molecules have been discovered recently. These include TIM-3, LAG3, TIGIT and BTLA.

T-cell immunoglobulin and mucin domain 3 (TIM-3) molecule is present on the surface of CD4 T cells, CD8 T cells, T regulatory cells and innate immune cells (dendritic cells, macrophages and natural killer cells). TIM-3 binds to specific ligands: galectin (Gal-9), phosphatidyl serine (PtdSer), high-mobility group box-1 protein (HMGB) and carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1). The interaction generates a variety of effects. These include apoptosis of effector T cells, suppression of T cells, suppression of innate immune response against tumor cells, suppression of anti-tumor activity and promotion of tumor growth[8]. In patients with malignancy, TIM-3 is upregulated. In pre-clinical studies, TIM-3 monoclonal antibody monotherapy showed modest anti-tumor activities[9] but combination of anti-TIM-3 and anti-PD-1/PD-L1 monoclonal antibodies produced significant anti-tumor response against a variety of malignancies which include colon cancer, lung cancer, ovarian cancer, melanoma, lymphoma, acute myelogenous leukemia and sarcoma[10].

LAG-3 (lymphocyte activation gene-3 protein) is an inhibitory receptor expressed on CD4, CD8, NK cells, B cells, and plasmacytoid dendritic cells[11-13]. It inhibits both activation and proliferation of T cells[14,15]. Anti-LAG3 monoclonal antibody can bind to LAG-3 present on tumor infiltrating lymphocytes (TILs), and prevent their binding with MHC (major histocompatibility complex) .class II molecules expressed on tumor cells. This may lead to activation of antigen-specific T lymphocytes and cytotoxic T-cell mediated tumor lysis. Clinical trials were done with different types of LAG-3 monoclonal antibodies (IMP321] on various malignancies-metastatic renal cell cancer, breast cancer, unresectable pancreatic cancer, advanced and unresectable melanoma[16].

T cell immunoreceptor with Ig and ITIM domains (TIGIT) is an inhibitory immunoreceptor present on some T cells (CD4, CD8), natural killer (NK) cells and Treg cells that contain Ig and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains. TIGIT ligands include CD155 and CD 112. In certain malignancies, CD155 and CD 112 are highly expressed on macrophages and dendritic cells. TIGIT ligation leads to inhibition of T cell proliferation and suppression of cytolytic function of NK cells[17]. Anti-tumor activity is suppressed by TIGIT primarily *via* Tregs and not CD8 T cells[18]. Anti-TIGIT monoclonal antibody as a monotherapy or in combination with anti-PD-L-1 antibodies have shown efficacy in anti-tumor activity[19] in phase I/II trials.

BTLA (B and T lymphocyte attenuator) also known as CD272 is an inhibitory protein functionally and structurally similar to CTLA-4 and PD-1. It is mainly expressed on immune cells, NK cells, dendritic cells and splenic macrophages. BTLA acts as a ligand for tumor necrosis factor receptor superfamily member 14 (TNFRSF-14) also known as herpes virus entry mediator (HVEM).

BTLA/HVEM complex inhibits T cell activation and proliferation[20]. In certain malignancies like leukemia and melanoma, BTLA is overexpressed. In mouse model, BTLA neutralizing antibody limited tumor growth[21]. Anti-human BTLA monoclonal antibody is currently in development.

**CURRENT CHECKPOINT INHIBITORS**

The current checkpoint inhibitors with their indications and schematic diagram (Figure 1) are mentioned below[22-28]: CTLA-4 blocker, PD-1 inhibitors, and PD-L1 inhibitors.

***CTLA-4 blocker***

**Ipilimumab:** Indications include melanoma with lymph node involvement, advanced melanoma, non-small cell and small cell lung cancer, advanced renal cell cancer, and hormone refractory prostate cancer. Great success with durable clinical benefit was seen with Nivolumab plus Ipilimumab combination when given in DNA mismatch repair-deficient/microsatellite instability–high metastatic colorectal cancer[29]

**Tremelimumab:** It is undergoing human clinical trials for the treatment of various malignancies but is not yet approved by the United States Food and Drug Administration (FDA).

***PD-1 inhibitors***

**Nivolumab:** Indications are melanoma with lymph node involvement, unresectable or metastatic melanoma, advanced renal cell carcinoma, advanced or metastatic urothelial cancer, metastatic non-small cell lung cancer and small cell lung cancer with progression after platinum based chemotherapy, refractory classical Hodgkin lymphoma, recurrent or metastatic squamous cell cancer of head and neck, microsatellite instability-high or mismatch repair deficient colorectal cancer, hepatocellular carcinoma.

**Pembrolizumab:** Indications include unresectable or metastatic melanoma, metastatic non-small cell lung cancer, advanced head and neck squamous cell carcinoma, advanced or metastatic gastric or gastroesophageal junction cancer, microsatellite instability-high cancer, locally advanced or metastatic urothelial cancer, recurrent or metastatic cervical cancer, refractory classical Hodgkin lymphoma, refractory primary mediastinal large B-cell lymphoma.

***PD-L1 inhibitors***

**Atezolizumab:**Indicated for advanced or metastatic non-small cell lung cancer, advanced or metastatic urothelial cancer.

**Avelumab:** Indicated for advanced or metastatic urothelial cancer, metastatic Merkel cell cancer.

**Durvalumab:** Indicated for advanced or metastatic urothelial cancer, unresectable, stage III non-small lung cancer.

**IMMUNE-RELATED ADVERSE EVENTS**

Immune-related adverse events (IRAE)can occur due to the use of checkpoint inhibitors. Inflammatory side effects generally involve the skin, gastrointestinal tract, liver and endocrine glands. The cardiovascular, pulmonary, renal, hematological and musculoskeletal system are less commonly involved. IRAE are more severe following administration of CTLA-4 inhibitor in comparison to PD-1 or PD-L1 inhibitors. The time of onset of IRAE is generally 1-6 mo after administration of checkpoint inhibitors[30]. We will be discussing here mainly the gastrointestinal, hepatic and pancreatic side effects of checkpoint inhibitors.

Immune-related adverse events are classified according to National Cancer Institute's Common Terminology Criteria for Adverse Events (AE), version 3.0[31]. Grade 1: Mild AE; Grade 2: Moderate AE; Grade 3: Severe AE; Grade 4: Life-threatening or disabling AE; Grade 5: Death related to AE.

***Gastrointestinal***

Diarrhea is the most common gastrointestinal side effect after administration of checkpoint inhibitors. Diarrhea occurs in 27%-31% of cases following CTLA-4 inhibitor therapy[32] and less than 4% of cases following anti-PD-1 and anti-PD-L1 therapy[33]. Diarrhea varies from mild to severe in intensity. Immune mediated mild to severe colitis, colon perforation and even death can occur following checkpoint inhibitor therapy[34,35]. Severe colitis can occur in 5% of cases following CTLA-4 inhibitor therapy and less than 2% of cases following anti-PD-1 therapy. The colitis may mimic Crohn’s colitis or ulcerative colitis, and can be associated with intra-abdominal abscess, anal fissure and fistula[36]. Pembrolizumab-induced collagenous colitis and lymphocytic colitis have also been reported in the literature[37,38].

***Management***

Mild diarrhea or grade I diarrhea with stool frequency less than 4 times per day can be managed conservatively without discontinuing checkpoint inhibitors. Stool for ova, parasites, giardia antigen, stool culture and C. difficile toxin should be sent to evaluate for any underlying infection. Patient should be given adequate oral hydration and anti-diarrheal agents. If diarrhea still persists for 5-7 d or gets worse, patients should be treated like cases of moderate diarrhea.

Moderate diarrhea or grade II diarrhea with stool frequency between 4-6 times per day should be managed by discontinuation of checkpoint inhibitors, ruling out infection by sending stool samples as mentioned above, giving adequate oral hydration and administering empiric treatment with oral corticosteroid (prednisone 1 mg/kg/d) with close clinical follow up[39]. Colonoscopy is not required if the patient responds to the above measures. 2-5 d after control of diarrhea, prednisone should be slowly tapered over 1-2 mo period of time. Trimethoprim-sulfamethoxazole should be given as a prophylaxis against opportunistic infection during the tapering period[40].

If the patient does not respond to the conservative measures or if the patient has severe diarrhea *i.e.*, grade III or IV diarrhea with stool frequency more than 6 times per day with severe and persistent abdominal pain, fever, rectal bleeding or ileus, intravenous hydration and intravenous steroid (methylprednisone 1-2 mg/kg/d) should be started[41]. Antidiarrheal agents like loperamide and lomotil

(diphenoxylate/atropine) should be avoided. Abdominal CT (computerized axial tomography) should be done to assess the severity and complications of colitis (perforation and peritonitis). Colonoscopy or flexible sigmoidoscopy should be done not only to evaluate the severity and extent of colitis but also to take random and targeted colon biopsy to rule out underlying cytomegalovirus (CMV) infection[35]. CMV colitis is diagnosed by characteristic histology (owl’s eye intranuclear inclusion bodies), CMV biopsy PCR (polymerase chain reaction) or CMV biopsy viral culture[42]. Colonoscopic findings may include loss of vascular markings, erythema, congestion, friability, ulcerations and spontaneous bleeding. The severity of diarrhea may not correlate with the colonoscopic or histologic findings.

Treatment should be continued until there is significant improvement of diarrhea *i.e.*, grade 0-1 diarrhea. If there is clinical response to corticosteroid, continue that for a month and slowly taper. If the patient’s diarrhea is refractory to steroid or colonoscopy shows severe colitis, multiple colon ulcers or pancolitis, anti-TNF therapy like Infliximab (5 mg/kg every 2 wk) or anti-integrin therapy like Vedolizumab (300 mg 0, 2, 6 wk) should be added[43-45]. Concomitant bacterial, viral or *Clostridium difficile* infection should be treated at the same time. Following resolution of symptoms, checkpoint inhibitors can be restarted if the benefits outweigh the risk, and if the daily dose of prednisone can be reduced to less than 10 mg per day without any other immunosuppressive medication.

***Summary of management of diarrhea***

Diarrhea onset approximately 6 wk after checkpoint inhibitor therapy: Assess severity of diarrhea and rule out infection by sending stool samples 🡪 Grade I diarrhea: Conservative treatment with oral hydration and anti-diarrheal agents 🡪 Persistence of diarrhea after 5-7 d 🡪 Manage as grade II diarrhea. Grade II diarrhea: Stop checkpoint inhibitor, start oral corticosteroid and continue oral hydration: (1) Clinical improvement 🡪 2-5 d after control of diarrhea, start tapering corticosteroid over 1-2 mo plus trimethoprim-sulfamethoxazole as prophylaxis; (2) no clinical improvement 🡪 Manage as grade III or IV diarrhea. Grade III or IV diarrhea: Hospitalization, parenteral hydration, parenteral corticosteroid, abdominal CT and colonoscopy: (1) Clinical response: Continue steroid for a month and taper; (2) no clinical response: Anti-TNF therapy.

***Hepatic***

Checkpoint inhibitors can cause immune-mediated hepatitis in less than 5% of cases taking these medications[46]. Although this can occur anytime while the patient is on checkpoint inhibitor therapy, most commonly it occurs 6-7 wk after the onset of therapy[47]. Most of the time patients remain asymptomatic with elevated serum transaminases. Sometimes, the hepatitis can be more severe, patient may present with fever, malaise, fatigue, hepatomegaly and hyperbilirubinemia. Acute viral hepatitis (HAV, HBV, HCV, EBV, CMV) and autoimmune hepatitis need to be excluded by serology and liver biopsy[48]. Predominant hepatic parenchymal injury with panlobular hepatitis or predominant bile duct injury with mononuclear cells infiltration around proliferated bile ductules can be seen after checkpoint inhibitor therapy[49]. Sometimes it is difficult to distinguish autoimmune hepatitis from drug-induced hepatitis. In autoimmune hepatitis intra-acinar and portal plasma cells with rosette formation and emperiopoisis are prominent whereas neutrophilic infiltration is more seen in drug-induced liver injury[50].

***Management***[51]

Grade 1 immune mediated hepatitis: Patient is asymptomatic or mildly symptomatic but Laboratory studies show AST/ALT: < 2.5 × ULN (Upper limit of normal) and total bilirubin: < 1.5 × ULN. Treatment: Continue checkpoint inhibitor therapy but monitor LFT.

Grade 2 immune mediated hepatitis: Patient is symptomatic (fever, malaise, fatigue) and Laboratory studies show AST/ALT: 2.5-5 × ULN and total bilirubin: 1.5-3 × ULN. Treatment: (1) Hold checkpoint inhibitor therapy; (2) viral hepatitis (HAV, HBV, HCV, HDV, CMV. EBV, HSV, VZV), autoimmune hepatitis and drug-induced hepatitis need to be ruled out[46]; (3) prednisone 1 mg/kg/d, taper the dose when patient’s symptoms improve; and (4) if symptoms do not improve after 48 h, alternate immunosuppressive agents like tacrolimus, mycophenolate mofetil or cyclophosphamide need to be considered.

Grade 3 or 4 immune mediated hepatitis: Patient is symptomatic as mentioned above and Laboratory studies show: AST/ALT: > 5 × ULN; Total bilirubin: > 3 × ULN. Treatment: (1) Hold checkpoint inhitors; (2) intravenous solumedrol 2-4 mg/kg/d. Taper the dose when patient’s symptoms improve; and (3) If symptoms do not improve after 5-7 d, tacrolimus 0.10-0.15 mg/kg/d should added. Alternative agents include, mycophenolate mofetil or cyclophosphamide.

***Pancreatic***

Immune mediated pancreatitis with pancreatic insufficiency has been reported few months after initiation of checkpoint inhibitor therapy[52]. Asymptomatic elevations of amylase and lipase can occur without fulfilling the diagnostic criteria of acute pancreatitis. As the clinical significance of this Lab abnormality is unknown, routine measurement of serum amylase and lipase is not recommended[53]. But if the patient is symptomatic with abdominal pain or nausea, immune mediated pancreatitis should looked for by checking amylase, lipase and imaging studies.

***Management***

Intravenous methylprednisolone (1 mg/kg/d) for few days followed by oral prednisone (1 mg/kg/d). Taper the dose when patients’ symptoms improve.

Pancreatic enzyme supplementation if there is evidence of pancreatic insufficiency (fecal elastase < 15 microgram/gm of feces).

**CONCLUSION**

Checkpoint inhibitors are novel forms of immunotherapy administered by the oncologists. Although they are extremely useful in various advanced and metastatic malignancies, they can cause multiple side effects. Gastroenterologists need to be aware of the various gastrointestinal, hepatic and pancreatic side effects which can be fatal if not managed early. Prompt recognition of these side effects, administration of systemic immunosuppressive therapy and supportive care could improve the clinical outcome without affecting the benefit of checkpoint inhibitors. Multidisciplinary team should be involved in the management of these side effects. As new checkpoints are being discovered and new checkpoint inhibitors are being developed, patients will be experiencing new IRAE. Management of those IRAE will improve as we gather more experience using new checkpoint inhibitors.

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PD-L1/ PD-1 CTLA-4 B7-1

APC

T cell

Tumor

cell

PD-L2 B7-2

**PD-L1 inhibitors:** **PD-1 inhibitors:** **CTLA-4 inhibitor:**

Atezolizumab Nivolumab Ipilimumab

Avelumab Pembrolizumab Tremelimumab

Durvalumab

**Figure 1: Schematic diagram of checkpoint inhibitors.**